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Steroid Hormones

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. EFFECTS OF ESTROGEN TREATMENT ON HUMAN TESTICULAR UNCONJUGATED STEROID AND STEROID SULFATE PRODUCTION IN VIVO.

Leinonen P, Ruokonen A, Kontturi M, Vihko R
Dept. Clinical Chemistry, Univ. Oulu, SF-90220 Oulu 22, Finland
J Clin Endocrinol Metab; 53(3):569-573 1981

To analyze the relationships between human testicular unconjugated and sulfate-conjugated steroids, we investigated the effects of estradiol [polyestradiol phosphate (E2)] and a synthetic estrogen [diethylstilbestrol diphosphate (DESDP)] on

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testicular, spermatic venous, and peripheral venous serum concentrations of these compounds. Six unconjugated steroids and four steroid su lfates were measured by specific RIAs after chromatography in 27 prostatic carcinoma patients without preceding endocrine therapy and in 29 patients castrated after E2 or DESDP treatment. E2 treatment decreased testicular concentrations of pregnenolone, testosterone (T), and 5 alpha-dihydrostestosterone (DHT). Testicular Androstenedione concentrations were also decreased, whereas progesterone concentrations increased, and there were decreased testicular concentrations of dehydroepiandrosterone sulfate (DHEA-SO4) and 5-androstene-3beta,17beta-diol sulfate. Spermatic venous concentrations of 17alpha-hydroxyprogesterone (17-OHP), T, and DHT as well as those of DHEA-SO4 and T sulfate were decreased after E2 treatment, and in the case of T, DHEA-SO4, and 17-OHP, this change was also reflected in peripheral serum concentrations. In the doses used, DESDP treatment was clearly more efficient than E2, and it decreased testicular concentrations and the secretion of all unconjugated and sulfated steroids. However, the difference between the effects of E2 and DESDP on peripheral serum steroid concentrations was mainly limited to those most clearly of testicular origin (17-OHP, T, and DHT). These findings show that estrogen treatment has an inhibitory effect on human testicular steroid sulfate production in vivo in addition to the known depressing effect on unconjugated steroid production. The results from E2-treated patients suggest that the changes in steroid sulfates are secondary to those in unconjugated steroids. The most probable sites of inhibition are a step before pregnenolone and the enzymes 17alpha-hydroxylase and 17-20-desmolase in the biosynthetic chain leading to T synthesis. (Author abstract) (37 Refs)

2. THE EFFECT OF 3-METHYLCHOLANTHRENE ON URINARY 6BETA-HYDROXYCORTISOL EXCRETION AND HEPATIC ENZYME ACTIVITY IN THE MARMOSET MONKEY (CALLITHRIX JACCHUS).

Challiner M, Park BK, Odum J, Orton TC
(c/o Park) Dept. Pharmacology and Therapeutics, Liverpool Univ., P.O. Box 147, Liverpool L69 3BX, England
Biochem Pharmacol; 30(15):2131-2134 1981

The effect of 3-methylcholanthrene treatment on the urinary excretion of 6beta-hydroxycortisol and hepatic enzyme activity was investigated in the marmoset monkey (Callithrix jacchus). 3-Methylcholanthrene increased cytochrome P-448 content, NADPH cytochrome-c reductase activity, 7-ethoxycoumarin O-deethylase activity and ethoxyresorufin O-deethylase activity but did not affect aminopyrine N-demethylase activity. This induction profile is qualitatively similar to that previously reported for the rat. There was no change in the ratio of urinary 6beta-hydroxycortisol to 17-hydroxycorticosteroids. The pattern of response to 3-methylcholanthrene indicates that cortisol 6beta-hydroxylase activity is not associated with induction of hepatic cytochrome P-488. (Author abstract) (8 Refs)

3. LUTROPIN-DEPENDENT PROTEIN PHOSPHORYLATION AND STEROIDOGENESIS IN RAT TUMOUR LEYDIG CELLS.

Bakker GH, Hoogerbrugge JW, Rommerts FF, Van der Molen HJ
Dept. Biochemistry, Div. Chemical Endocrinology, Medical Faculty, Erasmus Univ., Rotterdam, The Netherlands
Biochem J; 198(2):339-346 1981

Tumor Leydig cells have been incubated in the presence or absence of luteinizing hormone (lutropin). Stimulation of cells with lutropin (1,000 ng/ml) in the presence of 1-methyl-3-isobutylxanthine (0.25 mM) resulted in increased steroid production and increased protein phosphorylation. When pregnenolone metabolism was inhibited, basal pregnenolone production was 26.9 +-7.4 ng/60 min per 10(6) cells: stimulated production was 156.1 +-39.5 ng/60 min per 10(6) cells (means +- SD, n = 4). Lutropin-dependent phosphorylated proteins of molecular mass 17,000, 22,000, 24,000, 33,000 and 57,000 Da were detected. A significant increase of [32P]Pi incorporation into these phosphorylated proteins was observed concomitant with the increased pregnenolone production. The occurrence of the phosphoproteins in nuclei, mitochondria and postmitochondrial-supernatant was investigated. The 17,000 Da phosphoprotein was found in the nuclear fraction, whereas the 22,000, 24,000, 33,000 and 57,000 Da phosphoproteins were localized in the postmitochondrial-supernatant fraction. Of the cholesterol-side-chain-cleavage activity, 80.3 +-6.1% (mean +- SD, n = 5) was present in the mitochondrial fraction isolated from tumor Leydig cells, and this activity was 2.5-fold increased when cells had been preincubated with lutropin/1-methyl-3-isobutylxanthine (basal production: 194.6 +-28.6 ng/30 min per mg of protein; lutropin-stimulated production: 498.8 +-91.5 ng/30 min per mg of protein; means +- SD, n = 3). The similarities in the kinetics of the phosphorylation of proteins and the pregnenolone production after addition of lutropin/1-methyl-3-isobutylxanthine indicate that the phosphoproteins could be involved in the lutropin-dependent increase in steroidogenesis in tumor Leydig cells. It remains to be demonstrated, however, to what extent the phosphoproteins outside the mitochondria can influence the cholesterol-side-chain-cleavage activity inside the mitochondria. (Author abstract) (31 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

4. ASSOCIATION OF ENDOMETRIAL TUMORS WITH REPRODUCTIVE TRACT ABNORMALITIES IN THE AGED RAT.

Tang FY, Tang LK

Dept. Obstetrics, Biochemistry,, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY, 14642

Gynecol Oncol; 12(1):51-63 1981

The incidence of spontaneous tumors of the endometrium in Fischer 344 rats increases with age to a max of 55% at 32 mo (n = 22/40). The incidence of tumors was associated with an altered endocrine status in these aged rats. Forty-five percent of these endometrial lesions are associated with the presence of ovarian cysts. Vaginal cytology in all of the 31-mo-old rats bearing uterine tumors exhibited an acyclic or anestrus pattern. Serum levels of estradiol, testosterone, and LH were lower, whereas those of prolactin were higher in these aged rats than those of young rats. Pituitary cultures derived from the 31-mo-old animals exhibited an absence of estrogen-stimulated LH release which was present in cultures derived from cycling 9-mo-old Fischer rats. The data indicate a correlation between an anovulatory, acyclic reproductive pattern and etiology of these endometrial tumors. The aged Fischer rat may thus provide an animal model for the study of the hormonal etiology of this class of tumors. (Author abstract) (8 Refs)

5. MULTIPLE PLASMA STEROID RESPONSES TO GRADED ACTH INFUSIONS IN PATIENTS WITH PRIMARY ALDOSTERONISM.

Guthrie GP
Div. Endocrinology, Dept. Medicine, Univ. Kentucky Coll. Medicine, Lexington, KY, 40536
J Lab Clin Med; 98(3):364-373 1981

We measured the simultaneous responses of eight plasma steroids to the infusion of alpha 1-24 ACTH at incremental rates of 12.5 to 200 mIU/30 min in seven patients with primary aldosteronism (5 with adenomas, 2 with adrenal hyperplasia) and in 10 normal controls studied on regular sodium intakes and while supine. Patients with primary aldosteronism from adenomas had relatively higher concentrations (p less than 0.05) of aldosterone, 18 OH-B, corticosterone, and DOC than the two with hyperplasia and, save corticosterone, above the range of the normal controls. We found inconsistent differences in plasma progesterone, 17-hydroxyprogesterone, deoxycortisol, and cortisol. These findings suggest that the intermediate steps in aldosterone biosynthesis are hypersensitive to physiologic amounts of ACTH in patients with aldosterone-producing adenomas. Plasma levels of steroids distal to progesterone, ie, DOC, corticosterone, 18 OH-B, and aldosterone, are relatively higher after small amounts of ACTH in patients with adenomas than in normal subjects or those with adrenal hyperplasia. (Author abstract) (29 Refs)

6. CLINICAL SIGNIFICANCE OF PLASMA TESTOSTERONE LEVELS IN PATIENTS WITH DISSEMINATED GASTRIC CANCER.

Higuchi T, Nakamura T, Uchino H
Dept. Internal Medicine, Shiga Center for Adult Diseases, Shiga, Japan
Gan No Rinsho; 27(10):1210-1213,A-58 1981

Plasma testosterone levels and antipyrine half-time were measured in 17 men (61.4 +-7.3 yr old) with gastric cancer and 12 men (63.6 +-9.4 yr old) with hepatic cirrhosis (as controls) as a means to investigate enzyme activity in hepatic metabolism of drugs. Two of the patients were being treated with carbazilquinone, 5-fluorouracil, and cytosine arabinoside (QFC regimen). Plasma testosterone leve ls in the gastric cancer patients (8.19 +-4.08 nanog/ml) differed significantly with that of the controls (5.22 +-2.78 nanog/ml), but levels of serum albumin and cholesterol did not differ between the two groups. There were significant correlations between plasma testosterone and albumin levels and the plasma testosterone levels and patient survival time. Significant correlation was observed between plasma testosterone levels and antipyrine half-time in 12 of the patients with gastric cancer. Results suggested that decreased plasma testosterone levels and enzyme activities in hepatic metabolism of drugs which are observed in patients with disseminated gastric cancer may be related with low nutritional status, and administration of testosterone and anticancer steroids may be useful treatment for gastric cancer. (13 Refs) (In JPN)

7. MALIGNANCY ASSOCIATED WITH CONGENITAL ADRENAL HYPERPLASIA.

Duck SC
(c/o) Pediatric Endocrinology, 1700 W. Wisconsin Ave., Milwaukee, WI, 53233
J Pediatr; 99(3):423-424 1981

Four patients with 21-hydroxylase deficiency adrenal hyperplasia (HDAH) who developed a malignant tumor are described. These patients were among 42 children from 36 families diagnosed as having HDAH. The diagnosis of HDAH was based on both elevated 17-ketosteroid and pregnanetriol levels and depressed 17-hydroxycorticosteroid levels. By the time of diagnosis the perirectal malignancy, proven by biopsy in Patient 1, had metastasized to the lungs. The patient died within 2.5 mo. The other three patients were thriving at the time of report: Patient 2 was disease free; Patient 3 underwent repeated spinal surgery for tumor regrowth in 1979 and continues to grow along the 25th to 50th percentiles; Patient 4 was responding appropriately after 14-18 scheduled mo of chemotherapy. Patient 3 also had juvenile schizophrenia and trisomy of the proximal segment of the long arm of chromosome 13. The coexistence of neoplasms in children with HDAH is discussed. (9 Refs)

8. HORMONAL STATUS OF PATIENTS WITH OVARIAN CARCINOMA.

Merabishvili NV, Murav'eva NI, Kuz'mina ZV, Bassalyk LS, Kozachenko VP, Tupikina SN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):41-44 1981

The results of evaluation of the hormonal status of 75 patients with Stage III-IV ovarian carcinoma and 10 patients with benign ovarian tumors are reported. Prior to the treatment, the blood level of estriol in the patients in a 46-50 yr age group was almost 2x greater than that in the patients in 55-60 yr age group. The estradiol and progesterone level did not depend upon the age of the patients. The most pronounced increase of estriol level was recorded in the patients in menopause of 5-10 yr duration. Surgery and subsequent chemotherapy resulted in significant decrease of the estrogens and progesterone levels in the blood. This decrease was more pronounced in women in premenopausal period. (5 Refs) (In RUS)

9. PROLACTIN AND PLACENTAL HORMONES DURING PREGNANCY IN PROLACTINOMAS.

Batrinos ML, Panitsa-Faflia C, Anapliotou M, Pitoulis S
Dept. Endocrinology, Alexandra Hosp., Athens (Goudi 609), Greece
Int J Fertil; 26(2):77-85 1981

Levels of prolactin (PRL), estradiol, estriol, progesterone, placental lactogen, and chorionic gonadotropin were measured during pregnancy and early postpartum in three patients with prolactinoma. Pregnancy had been achieved by (1) bromocriptine treatment, (2) irradiation of the pituitary, or (3) human gonadotropin treatment after excision of the tumor. Case 1 showed high pretreatment levels of PRL, which were reduced by the bromocriptine treatment. PRL again climbed to pretreatment level in the 2nd mo of pregnancy, followed by another increase after the 30th wk. PRL level dropped just before labor, which occurred 1 wk after a severe headache and dizziness. It further declined postpartum. PRL in case 2 was reduced, but not to normal levels, by treatment; it remained slightly raised during pregnancy. PRL in case 3 remained in the low normal range throughout pregnancy and early postpartum. Patients 2 and 3 gave birth to normal twins. Placental hormones were normal in all cases. Estradiol and progesterone reached higher levels late in pregnancy in the cases with twins. Agalactia occurred in all three cases. Results indicate that PRL measurements reflect changes in prolactinomas, maternal hyperprolactinemia or failure of PRL to increase during pregnancy does not affect placental hormone secretion or amniotic fluid PRL, and hyperprolactinemia during pregnancy is of maternal pituitary origin. (30 Refs)

10. IN VIVO REGULATION OF OVARIAN ACTIVITY BY ALPHA-FETOPROTEIN.

Aussel C, Lafaurie M, Masseyeff R, Stora C
Faculte de Medicine, Inserm U210, Chemin de Vallombrose, 06034 Nice Cedex, France
Steroids; 38(2):195-204 1981

Adult female rats, each injected with 760 ug alpha-fetoprotein (AFP) weekly, presented after the 3rd wk a decrease of ovarian activity evidenced by a decreased number of maturing follicles, corpora lutea, and a drop in ovarian wt. The level of progesterone was low and agreed with the deceased number of corpora lutea. Conversely, total and free estradiol-17beta levels remained normal despite the known ability of AFP to bind estrogenic hormones. A regulatory role of AFP during the postnatal stage of sexual maturation is proposed. (Author abstract) (27 Refs)

11. ELEVATED URINE ESTROGEN AND PREGNANEDIOL LEVELS IN DAUGHTERS OF BREAST CANCER PATIENTS.

Trichopoulos D, Brown JB, Garas J, Papaioannou A, MacMahon B
(c/o MacMahon) Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115
JNCI; 67(3):603-606 1981

Urine levels of three major estrogens and of pregnanediol were measured for 76 nulliparous daughters of breast cancer patients and for 115 control women of similar age and parity. Concentrations of estrone and estradiol tended to be higher in the daughters of breast cancer patients than in the controls; total estrogens were elevated in both phases of the menstrual cycle and significantly so in the luteal phase. There was little difference between the daughters and the controls in estriol ratios-the ratios of the concentration of estriol to the sum of the concentrations of estrone and estradiol. Pregnanediol levels were higher in the daughters than in the controls. (Author abstract) (12 Refs)

12. STUDIES ON THE INTERRUPTION OF THE TESTICULAR TESTOSTERONE PRODUCTION THROUGH THE TESTICLES IRRADIATION IN PROSTATE CANCER PATIENTS.

Fleck H, Stahl F, Mau S
Urologische Klinik, St.-Hedwigs-Krankenhaus, Grosse Hamburger Strasse, DDR-1040 Berlin, E. Germany
Z Urol Nephrol; 74(6):443-446 1981

The 11 prostate cancer patients 68-78 y old received 20 Gy (5 x 2 Gy per wk) irradiation of the testicles. The plasma testosterone levels decreased on the av to 70.3% of the initial values, but they decreased to only 5% of the initial value after orchiectomy. It is evident that the irradiation cannot replace the therapeutic value of the orchidectomy. The higher irradiation doses can cause increased skin damage and can be themselves potential carcinogens on the irradiated area. (20 Refs) (In GER)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

13. STUDIES ON SPECIFIC MARKERS OF HORMONE-DEPENDENCE IN ENDOMETRIAL CARCINOMA: ESTRADIOL RECEPTORS AND UTERINE PEROXIDASE.

Morikawa S, Sekiya S, Takamizawa H
Dept. Obstetrics and Gynecology, Sch. Medicine, Chiba Univ., Inohana, Chiba 280, Japan
Nippon Sanka Fujinka Gakkai Zasshi; 33(3):339-343 1981

Both cytosol estradiol-17beta (E2) receptors and uterine peroxidase were detected in normal uterine tissues of rat and hamster, however, they were not detected when the tissues were cultivated in vitro. Uterine peroxidase was specifically induced by the administration of E2 in these normal uterine tissues in vivo. On the other hand, malignant tissues formed by the transplantation of uterine and mammary adenocarcinoma cells showed hormone-independence. Neither cytosol E2 receptors nor peroxidase were detected in these malignant tissues. These results indicate that, in addition to E2 receptors, peroxidase induction by E2 is a specific marker for hormone-dependence in both normal and abnormal uterine tissues. (Author abstract) (20 Refs) (In JPN)

14. COMPARISON OF DEXAMETHASONE BINDING AND RESISTANCE TO INHIBITION OF INDUCED DIFFERENTIATION IN SUBCLONES OF MURINE ERYTHROLEUKEMIA CELLS.

Osborne HB
Laboratoire de Biologie Moleculaire et Cellulaire, Centre d'Etudes Nucleaires de Grenoble 85X, E.R. 199 du C.N.R.S., Departement de Recherche Fondamentale, F 38041 Grenoble, France
Biochem Biophys Res Commun; 101(3):823-829 1981

Dexamethasone (DEX) binding to subclones of the murine erythroleukemia cell line DS 19 having different sensitivities to DEX inhibition of hexamethylene bisacetamide (HMBA)-induced differentiation was characterized. Differentiation was assessed via benzidine staining for Hb. One clone (B6) was sensitive to DEX inhibition and the other clone (D1) was semi-resistant: D1 differentiation was only 40% inhibited at 1uM DEX. Scatchard analysis of the total amount of 3H-DEX specifically bound/intact cell yielded the following for B6 and D1, respectively: dissociation constant (Kd) = 5 +-1 and 14 +-1 nanoM, and number of binding sites/cell (n) = 34,000+-5,000 and 54,000+-5,000. Hence at less than 1 nanoM DEX the sensitive B6 cells bind more DEX due to greater affinity, but at greater than 10 nanoM the D1 cells bind more due to greater binding site number. Resistance of D1 cells to DEX inhibition appeared not to result from less DEX binding/cell. As in intact cells, the total amount of 3H-DEX specifically bound to B6 and D1 nuclei was nearly identical (12 femtomole/10(6) nuclei in the presence of 10 nanoM DEX). The time course of binding was also similar. For B6 cells cultured in 4 milliM HMBA and 10 nanoM 3H-DEX, where differentiation is inhibited, no additional retention of bound DEX occurred relative to that retained in the semi-resistant D1 cells. Resistance to DEX inhibition of HMBA-induced differentiation in the D1 subclone appeared not to be correlated with a reduction in the total or nuclear binding of DEX, but possibly with a defect at an event after binding of hormone-receptor complexes to chromatin. (16 Refs)

15. COMPARISON OF ESTRADIOL RECEPTOR INVESTIGATIONS AND HISTOCHEMICAL INVESTIGATIONS ON ENZYMES IN HUMAN MAMMARY CANCERS.

Gorlich M, Hecker D, Heise E
Dept. Experimental, Clinical Endocrinology, Central Inst. Cancer Res., Berlin, W. Germany
JNCI; 67(3):521-527 1981

The best way to predict the responsiveness of human breast carcinomas to hormone therapy is to investigate the estradiol receptor-binding abilities of these tumors. This binding induces many hormone-regulated changes in the activities of several enzymes. Therefore, enzyme activities after short-term organ culture exposed to added hormones were tested to see whether a correlation of enzyme activities exists with estradiol receptor binding. The results from both the estradiol receptor investigations and histochemical investigations on enzymes revealed a high degree of conformity, which confirms the existence of such a correlation. However, for this reason histochemical investigations on enzymes cannot eliminate the dis crepancy between the experimentally verified existence of estradiol receptor binding and the response of mammary tumors to hormone therapy, which is not higher than 50-60%. (Author abstract) (19 Refs)

16. OESTROGEN RECEPTOR ASSAY AND MORPHOLOGY OF BREAST CANCER.

Roberts AN, Hahnel R
(c/o Hahnel) King Edward Memorial Hosp. for Women, Bagot Road, Subiaco, Western Australia 6008
Pathology; 13(2):317-325 1981

The associations between estrogen receptors, several morphological features and prognosis were studied in 53 cases of primary breast carcinoma. There was no significant association between estrogen receptors and any morphological property studied (histological grade, cellularity, fibrosis, elastosis, necrosis, lymphatic permeation, follicular hyperplasia, encapsulation, vascular invasion, tubular areas, histiocytosis, lymphocytic cell infiltration, number of invaded lymph nodes, tumor size, site of recurrence). Disease-free interval and survival were longer in patients having cancers with positive estrogen receptors. Good prognostic signs were low histological grades, tubular areas and absence of lymphatic invasion within the primary tumor. (Author abstract) (22 Refs)

17. TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITIES AND GLUCOCORTICOID RECEPTORS IN LEUKAEMIA.

Sasaki R, Takaku F, Aoki T, Bollum FJ, Saito T, Dan S
Dept. Haematology, Jichi Medical Sch., 3311-1 Yakushiji Minamikawachi-Machi, Kawachigun, Tochigi 329-04, Japan
Br J Cancer; 44(1):63-67 1981

The relation between terminal deoxynucleotidyl transferase (TdT) activity, glucocorticoid (GC) receptors and the effect of vincristine-prednisolone (VP) therapy on fresh leukemia cases was examined. Five of six TdT+ leukemias showed high levels of GC receptors and a favorable response to VP therapy, whereas one acute lymphoblastic leukemia and three of chronic myelogenous leukemia cases in blast crisis with no TdT activity showed low level of GC receptors and poor response to VP therapy. Significant correlation (r = 0.821, p less than 0.01) was observed between TdT activity and the number of GC receptor sites in these cases. Chi square test showed significant difference (p less than 0.01) between TdT+ and TdT- leukemias in the effect of VP. A significant difference (p less than 0.01) was also observed between VP-effective and ineffective leukemias in the number of GC-receptor sites by unpaired t test. Therefore GC receptors may be responsible for the effect of VP on TdT+ leukemias. (Author abstract) (18 Refs)

18. EVIDENCE THAT ESTROGEN-RECEPTOR-NEGATIVE, PROGESTERONE-RECEPTOR-POSITIVE BREAST AND OVARIAN CARCINOMAS CONTAIN ESTROGEN RECEPTOR.

Sarrif AM, Durant JR
Dept. Pharmacology, Univ. Alabama Birmingham Sch. Medicine, P.O. Box 191, Univ. Station, Birmingham, AL, 35294
Cancer; 48(5):1215-1220 1981

A small number of primary metastatic breast carcinomas are estrogen-receptor-negative and progesterone-receptor-positive (ER-, PGR+) under the normal ligand-binding assay or sucrose density gradient conditions. Among more than 500 tumors analyzed in this laboratory over a yr and a half, 28 cases fit this category, 18 of which were patients 51 yr of age or younger (Group A) and 7 were patients over the age of 56 (Group B). The ages of three patients were unknown (Group C). By treatment of each of those tumor cytosols with dextran-coated charcoal before the assay was done, 13 of group A became positive (ER range 10-87 fmol/mg protein), 1 was borderline (ER 3-9 fmol/mg protein), 1 became positive only on sucrose gradient determination, and 2 remained negative. In comparison, two patients in Group B shifted from borderline ER to ER+ and only one ER- became ER+ at 10 fmol/mg protein. The data provide additional rationale for determining both ER and PGR in all patients, and have obvious implications for the need for standard methods of determining ER and PGR in the prognosis of women with breast cancer. (Author abstract) (19 Refs)

19. GLUCOCORTICOID RECEPTOR DETERMINATION IN LEUKEMIA PATIENTS USING CYTOSOL AND WHOLE-CELL ASSAYS.

Iacobelli S, Natoli V, Longo P, Ranelletti FO, De Rossi G, Pasqualetti D, Mandelli F, Mastrangelo R
Lab. Molecular Endocrinology, Sacro Cuore Catholic Univ., 00100 Rome, Italy
Cancer Res; 41(10):3979-3984 1981

Parallel determinations of glucocorticoid receptors in the cells of patients with various forms of leukemia were made by two assay methods, one using cell-free cytosolic extracts and the other using whole-cell preparations. Both assays revealed saturable binding of triamcinolone acetonide in all cases. The mean equilibrium dissociation constant for the interaction of triamcinolone acetonide with the cytoplasmic receptor at 2 C was 9.45 +-6.33 (S.D.) nM while that for the whole-cell binding at 37 C was 6.13 +-3.25 nM, suggesting an increase in receptor affinity at physiological temperatures. Competition experiments with various unlabeled steroids revealed a higher degree of glucocorticoid specificity at 37 C in whole-cell suspensions than at 2 C in cytosol. In a comparative analysis of 41 leukemic cell specimens, it was found that determinations carried out by whole-cell assay, calculated as number of sites per cell, correlated well with those performed by cytosol assay, calculated as fmol/mg protein, independent of the type of leukemia. However, for cells with low receptor content, the two assay methods were more difficult to compare. In agreement with previous reports, the cytosol assay consistently underestimated the number of receptors with respect to the whole-cell assay, particularly in cases of lymphatic leukemia. Furthermore, the underestimation decreased for increasing levels of total cellular receptor. These results suggest that, in addition to possible defects in the cytoplasm-to-nucleus translocation process, the acceptor-binding capacity of the nucleus may also represent one of the factors which determines the levels of assayable cytoplasmic receptors. Moreover, they indicate that the two assay methods furnish nonequivalent information. (Author abstract) (28 Refs)

20. PROGNOSTIC VALUE OF CONCANAVALIN A REACTIVITY OF PRIMARY HUMAN BREAST CANCER CELLS.

Furmansk P, Kirkland WL, Gargala T, Rich MA, Breast Cancer Prognostic Study Clinical Associates
Dept. Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(10):4087-4092 1981

A prospective, double-blind study was carried out to determine whether reactivity with concanavalin A (Con A) of human breast cancer cells was related to early disease recurrence. Mammary epithelial cells were isolated from 138 primary human breast cancers. The cells were placed in culture, and their reactivity with Con A was determined with a hemadsorption assay in which human RBC treated with various concentrations of Con A were incubated with the test (mammary epithelial) cells in situ. The Con A half-max value was determined as the concentration of Con A at which approx 50% of the target cells adsorbed RBC. Con A reactivity of the tumors was classified as high or low (half-max value less than or equal to 30 or greater than 30 ug/ml, respectively). Patients were followed for 2 to 60 mo after primary surgery (median, 22 mo). Those patients having tumors that were highly reactive with Con A were at significantly greater risk of developing early recurrence of their cancers than were those patients with low-reactivity tumors. No correlation was found between Con A reactivity and the age of the patients, their menopausal status, the number of axillary lymph nodes infiltrated with tumor, the estrogen receptor content of the tumor, or the clinical stage of the disease. These data show that Con A reactivity is an independent discriminator for identifying those breast cancer patients who are at high risk of developing early recurrent disease. (Author abstract) (28 Refs)

21. THYROID HORMONE RECEPTORS IN HUMAN BREAST CANCER.

Cerbon MA, Pichon MF, Milgrom E
Groupe de Recherches sur la Biochemie Endocrinienne et la Reproduction, INSERM U. 135, Faculte de Medicine Paris-Sud, 94270 Bicetre, France
Cancer Res; 41(10):4167-4173 1981

Optimum conditions were established for preparation of nuclei from human breast cancer biopsies. Incubation of nuclei with various concentrations of of L-3,3',5-[125I]triiodothyronine showed the presence of three binding systems: a high-affinity binding system (Type I) (KD approx 1.5 nM); an intermediate-affinity saturable system (Type II) (Kd approx 0.5 um); and a nonsaturable nonspecific system. Salt at high concentrations (0.4 M-KCl) extracted only Type I triiodothyronine-binding protein, thus simplifying its study and quantification. Type I binding protein was shown to have the affinity for triiodothyronine and the hormonal specificity usually ascribed to thyroid hormone receptors. Its sedimentation coefficient was 3.6S at 0.4 M KCl. Extractable triiodothyronine receptor was measured in 58 individual biopsies of primary and metastatic breast cancer. It was present in all tumors, but its concentration was highly variable (0.20 pmol/mg DNA; range, 0.044 to 0.702). Triiodothyronine receptor concentration was not correlated with age or endocrine status of the patient or with extension or histological grading of the tumor. Moreover, there was no correlation with estradiol and progesterone receptor concentrations. (Author abstract) (38 Refs)

22. MEASUREMENT OF PROGESTERONE RECEPTORS IN HUMAN BREAST TUMORS: COMPARISON OF VARIOUS METHODS OF ANALYSIS.

Namkung PC, Petra PH
Dept. Lab. Mediciney Dept., Univ. Washington Sch. Medicine, Seattle, WA, 98195
J Steroid Biochem; 14(9):851-854 1981

The measurement of estrogen and progesterone receptors in human breast tumors is important to the successful management of the patients. These receptors exist in two macromolecular forms that have different sedimentation coefficients: 4S and 8S. Progesterone receptors were measured simultaneously in freshly prepared tissue cytosols from 10 individual tumors by three methods: the single-saturating dose (SSD) analysis, the sucrose density gradient method, and the multi-point Scatchard plot analysis. All three methods agreed extremely well for the determination of total (4S + 8S) receptor concentration; there was no loss of receptor-binding activity during the time required for sucrose density gradient analysis. The two macromolecular forms of the receptor appear to have similar if not identical dissociation constants because receptor concentrations calculated by extrapolation of linear Scatchard plots are identical to those obtained from either the summation of 4S and 8S areas of the density gradients or the SSD analysis. All three tested methods can be used in clinical measurements of the progesterone receptor. (14 Refs)

23. 1,25-DIHYDROXYVITAMIN D3 SPECIFICALLY BINDS TO A HUMAN BREAST CANCER CELL LINE (T47D) AND STIMULATES GROWTH.

Freake HC, Marcocci C, Iwasaki J, MacIntyre I
Endocrine Unit, Royal Postgraduate Medical Sch., Du Cane Road, London, W12 OHS, England
Biochem Biophys Res Commun; 101(4):1131-1138 1981

The binding of the active vitamin D3 metabolite 1,25-dihydroxyvitamin D3 (DHD) to receptors on T47D breast carcinoma cells in vitro was studied. A specific receptor with a dissociation constant of 1.1 x 10(-10), a sucrose gradient sedimentation coefficient of 3.7S and a frequency of 15,000 sites/cell was identified. Growth of T47D cells was enhanced by DHD in a dose-dependent manner at physiological doses up to 0.8 nanoM. At higher doses the effect was eliminated. Growth was also enhanced by estradiol. Metabolites of vitamin D3 showing affinity for the binding sites, in decreasing order of affinity, were the 1,25-dihydroxy, 1,24,25-trihydroxy, 25 hydroxy, and 24,25-dihydroxy derivatives. The new metabolite 1beta,25-dihydroxyvitamin D3 had the same affinity as the 24,25 dihydroxy metabolite. The binding site was retained in culture cell lines from the parental tissue. The in vivo significance of vitamin D3 effects on breast cancer cells is unknown. (15 Refs)

24. STUDIES ON THE INDICATORS FOR THE RESPONSIVENESS OF HUMAN BREAST CANCER TO SEX STEROIDS.

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Dept. Obstetrics and Gynecology, Kyoto Prefectural Univ. Medicine, Kyoto 602, Japan
Nippon Naibunpi Gakkai Zasshi; 57(1):64-88 1981

Characteristics of steroid receptors in breast cancer were investigated to determine indicators of response to treatment for breast cancer. First, steroid receptors in breast cancer tissues were characterized by means of dissociation constants in tissues from premenopausal and postmenopausal patients; dissociation constants were determined with the aid of charcoal absorption at 4 C for estradiol-17beta-estrogen receptors (ERs), R5020-progesterone (PR) receptors, 5alpha-dihydrotestosterone (DHT)-androgen receptors (ARs), and R1881-ARs. These receptors sedimented to 7-6S and 5-4S regions; the 7-6S binding was easily dissociated with 5-20% sucrose gradient centrifugation. ARs and PRs were contained in the R1881-cytosol bindings. Cytosolic steroid receptor levels were analyzed in each case, and max binding sites were analyzed by Scatchard plot analysis. Nuclear receptors were determined by exchange assay; nuclear PRs and ARs were detected in a few cases, and nuclear ERs were detected while cytosolic ERs were not detected. Results of studies of nuclear binding of steroid receptor complexes substituting ERs and PRs of rabbit uterine cytosol for the human breast cancer tissues suggested that part or all of the nuclear receptor-binding sites of breast cancer tissues are defective in some tumor nuclei. The existence of receptors in the cytosol or nuclei, nuclear binding of receptor-steroid complexes, or measurement of nuclear RNA synthesis by steroid receptors in breast cancer cells were thought to be effective indicators of the endocrine-therapy response of breast cancer. (34 Refs) (In JPN)

25. OESTROGEN RECEPTOR PROTEINS IN MALIGNANT AND FETAL PANCREAS.

Greenway B, Iqbal MJ, Johnson PJ, Williams R
Liver Unit, King's Coll. Hosp., Medical Sch., London SE5 8RX, England
Br Med J; 283(6294):751-753 1981

High levels of high-affinity estrogen binding were detected in cytosolic and nuc lear fractions of tumor tissue from six patients with pancreatic carcinoma. Similar binding was found in fetal but not in normal adult pancreas, making derepression of fetal genes a possibility. Specific androgen binding was not detectable. These findings suggest that anti-estrogen treatment may offer a new approach to the treatment of pancreatic carcinoma. (Author abstract) (20 Refs)

26. RELATIONSHIP BETWEEN ESTROGEN RECEPTORS AND CLINICAL-MORPHOLOGICAL CHARACTERISTICS OF PRIMARY BREAST CANCER.

Vishniakova VV, Ermilova VD, Murav'eva NI, Bassalyk LS
Dept. Breast Tumors, All-Union Res. Cancer Center, Moscow, USSR
Arkh Patol; 43(7):20-23 1981

The level of estrogen receptors (ER) was studied in 139 specimens of breast cancer. Of 139 patients, 101 were found to have ER-positive tumors (65% of the premenopausal patients and 81% of the patients in the menopause). The level of ER did not depend upon tumor histology, degree of malignancy, or the treatment modality. (12 Refs) (In RUS)

27. NUCLEAR AND CYTOPLASMIC OESTROGEN RECEPTORS IN SQUAMOUS CARCINOMA OF THE CERVIX.

Soutter WP, Pegoraro RJ, Green-Thompson RW, Naidoo DV, Joubert SM, Philpott RH
Dept. Gynaecology, Univ. Sheffield, Jessop Hosp. for Women, Sheffield S3 7RE, England
Br J Cancer; 44(2):154-159 1981

Nuclear and cytoplasmic estrogen receptors (REN and REC) were sought in five normal cervices and in 43 specimens of squamous carcinoma of the cervix. All three tissue components of the five normal cervices contained both REN and REC. Thirty-five (81%) of the tumors contained receptors, but in only 9 (21%) were they found in both subcellular compartments. Twenty-four tumors (56%) had only REC and 2 had only REN. The potential therapeutic significance of these findings is not yet known, but it seems possible that tumors with an intact receptor mechanism might benefit from estrogen therapy and have a more favorable prognosis. (Author abstract) (19 Refs)

28. GLUCOCORTICOIDS AND BENZO(A)PYRENE HAVE OPPOSING EFFECTS ON EGF RECEPTOR BINDING.

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Nature; 293(5831):404-406 1981

Epidermal growth factor (EGF)-receptor binding was used as a marker for membrane effects in C3H10T1/2 mouse embryo fibroblasts exposed to the potent glucocorticoid fluocinolone acetonide (FA), and to the carcinogens benzo(a)pyrene (BP), and 12-O-tetradecanoyl-phorbol-13-acetate (TPA). FA alone produced a 1.9x stimulation of EGF-receptor binding over that observed in control cultures. The stimulation was apparent within 1 hr and reached a max by 24 hr. FA pretreatment (2 x 10(-7) M) protected the cells from the approx 50% inhibition of EGF-binding induced by BP (2 x 10(-6) M) or TPA (10(-9) M). Results suggested that glucocorticoids inhibit carcinogenesis by inducing cell membrane changes that are reciprocal to those induced by carcinogens and tumor promotors. (22 Refs)

29. HORMONE RECEPTORS IN MALE BREAST CARCINOMA.

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J Surg Oncol; 18(1):55-59 1981

It is well established that approx 60% of female breast cancers contain estrogen receptors (ER+). The hormonal receptor status of male breast cancers remains relatively unknown. Tumor tissue from 14 patients has been reviewed at the University of Oregon Health Sciences Center. Specimens of all 14 patients were ER+ with a range of 5.5 to 374 fmol/mg protein. Eight of 12 patients had tumors which also contained progesterone receptors (PR+) with a range of 42 to 1,852 fmol/mg/protein. Nine patients were treated by modified radical mastectomy, two by radical mastectomy, one by simple mastectomy, and two by biopsies only. Twelve patients remain free of disease with a mean follow-up of less than 2 yr. The two patients who developed metastases both responded to endocrine ablation by orchiectomy and subsequent adrenalectomy. These data suggest that male breast cancer is highly endocrine sensitive and that endocrine ablation can play an integral part in those men unfortunate enough to develop disseminated disease. (Author abstract) (18 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

30. EPIDERMAL GROWTH FACTOR INITIATES DNA SYNTHESIS AFTER A TIME-DEPENDENT SEQUENCE OF REGULATORY EVENTS IN SWISS 3T3 CELLS: INTERACTIONS WITH HORMONES AND GROWTH FACTORS.

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Friedrich Miescher-Inst., CH-4002, Basel, Switzerland
J Cell Physiol; 108(2):145-153 1981

Swiss mouse 3T3 cells in confluent and quiescent cultures were treated with epidermal growth factor (EGF) in various single and split doses and in combinations with insulin, hydrocortisone, prostaglandin E1 (PGE1), and prostaglandin F2 (PGF2). DNA synthesis was assayed using radioactive labeling. EGF stimulated the synthesis of DNA in quiescent cultures after a lag period of about 15 hr. The final rate of initiation of synthesis followed first-order kinetics and was quantified by a rate constant k. The value of k was affected by administrations of EGF during the prereplicative period. The minimum length of the lag phase was set by the first dose of EGF, independent of concentration, while k was dependent on concentration. Insulin alone did not stimulate DNA synthesis. In combination with EGF it showed a synergistic effect. Insulin did not effect the length of the lag phase. Hydrocortisone, when added within 8 hr of the addition of EGF or EGF plus insulin, inhibited the stimulatory effects of those substances. PGE1 inhibited DNA synthesis by increasing the lag phase. PGF2 had a synergistic effect in combination with EGF. The results suggest that a growth factor first induces a sequence of regulatory events leading to the initiation of DNA synthesis. Then it acts separately to regulate the rate of DNA synthesis. Prostaglandin and EGF apparently act on different regulatory events. (29 Refs)

31. INHIBITION OF TYROSINE AMINOTRANSFERASE INDUCTION BY UTP DEFICIENCY AND ITS REVERSAL BY 5-FLUOROURIDINE IN CULTURED HEPATOMA CELLS.

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Biochim Biophys Acta; 655(1):34-40 1981

Hepatoma tissue culture cells, grown in the presence of D-galactosamine and 6-azauridine, demonstrate a strong reduction of the intracellular UTP pool that can be replenished by formation of UTP from uridine and FUTP from 5-fluorouradine within 2 hr. Concomitantly with the UTP deficiency, a decrease of dexamethasone-induced tyrosine aminotransferase activity occurs. 5-Fluorouridine, as compared to uridine, is even more efficient in restoring the activity of tyrosine aminotransferase. Treatment of the cells with D-galactosamine alone results in a minor lowering of UTP that is not followed by the inhibition of the enzyme induction. However, the administration of D-galactosamine, simultaneously or at any time up to 5 hr before or after dexamethasone, leads to a 1.5-to two-fold higher induction (superinduction) which appears 24 hr later. (Author abstract) (39 Refs)

32. ESTABLISHMENT OF CULTURED DD/TBR MOUSE MAMMARY TUMOR CELL LINES.

Iwai Y
Central Res. Inst., Radiation Center of Osaka Prefecture, Osaka, Japan
Nara Igaku Zasshi; 32(2):168-180 1981

Three mouse mammary gland cultured cell lines were established from a mammary carcinoma that spontaneously occurred in a 10-mo-old female DD/Tbr strain mouse. Two of the cell lines were epithelial (DD-762 and DD-763) type cells and one was spindle-shaped (DD-761). Except for the DD-764 cell line, the chromosome number was 80 and the population doubling time was 18 hr. These cell lines were thought to produce B-type RNA virus (MuMTV) and not murine leukemia virus (MuLV). Study of viral kinetics by means of RNA-directed DNA polymerase (RDDP) activity assay indicated that MuMTV production was observable during the stationary phase but not the logarithmic phase of cell growth. The production of the mammary tumor virus was found to be inversely dependent upon the presence of dexamethasone (DXM); MuMTV was produced in large amounts (0.8 mg viral protein/liter/day in DD-764), and the production was enhanced with the addition of DXM. (27 Refs) (In JPN)

33. ROLE OF TESTOSTERONE ON MITOMYCIN C INDUCED CHANGES IN TESTICULAR HISTOLOGY IN RATS.

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Indian J Exp Biol; 19(4):386-387 1981

The role of testosterone in mitomycin C (MC)-induced changes in testicular histology was studied in closed colony-bred sexually immature male rats. The data clearly showed that testicular wt was greatly reduced in MC-treated rats but was near normal in those MC-treated rats who had also received testosterone proprionate. It was suggested that testicular degeneration in MC-treated rats was not only due to damage of the genetic material in the spermatogonia but also related to testosterone physiology. (12 Refs)

34. PARALLELISM BETWEEN THE EFFECT OF CORTISONE ACETATE ON HYBRID RESISTANCE AND NATURAL KILLING.

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Exp Hematol; 9(7):766-774 1981

We have studied the effect of cortisone acetate (CA) on two important biological functions: (1) on NK cell-mediated cytotoxicity of B6D2F1 mice to T cell lymphoma, YAC-1 and (2) on hybrid resistance of mice to parental B6 bone marrow grafts. Results of our experiments have shown that 5 mg of CA administered ip was effective in significantly decreasing NK cell cytotoxic potential. The effect of CA was prompt, since a significant decrease in NK cell cytotoxicity was observed already 3 hr after CA administration. This effect was, however, rather short-lasting since the NK cell cytotoxicity of CA-treated mice was comparable to that of control mice 120 hr after treatment. As to the mechanism of NK cell decrease, it appears that CA affected NK cell cytotoxicity directly, since the attempts to identify suppressor cells in CA-treated mice failed. Because NK cells and bone marrow effector (BME) cells were shown to bear close resemblance, we have investigated also whether a decrease in NK cell cytotoxicity would be reflected by a decline in BME cells rejection potential. Indeed, when resistant B6D2F1 hybrid mice were pretreated with 5 mg of CA, 48 hr before transplantation of 10(6) B6 parental bone marrow cells, the growth of B6 marrow cells was detected 7 or 8 days later in the spleens of B6D2F1 hybrid mice. These experiments indicated that bone marrow rejection potential was also weakened by CA treatment, and moreover, demonstrated further correlation between BME cells and NK cells. (Author abstract) (23 Refs)

35. POSSIBLE ASSOCIATION OF ANGIOSARCOMA WITH ORAL CONTRACEPTIVE AGENTS.

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Med J Aust; 1(9):473-474 1981

Angiosarcoma of the liver has been reported to be associated with the long-term use of androgenic-anabolic and estrogenic steroids. It has been suggested that this tumor might develop in women after long-term exposure to oral contraceptive steroids, although this association has not yet been reported. We present here the clinical and pathological findings in a 42-yr-old woman who died of hepatic angiosarcoma after taking oral contraceptive steroids for 10 yr. (Author abstract) (13 Refs)

36. HEPATOCELLULAR CARCINOMA INDUCED BY ESTROGEN AND PROGESTOGEN: DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN RATS FOLLOWING ORAL ADMINISTRATION OF SYNTHETIC ESTROGEN AND PROGESTOGEN.

Higashi S
First Dept. Surgery, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 30(3):295-303 1981

Female Wistar rats were given daily 0.075 mg of ethinyl-estradiol (EES) and 6 mg of norethindrone acetate (NEA) dissolved in olive oil by gavage for 1 yr, another group received similar treatment for 18 mo, and a third group received olive oil alone for 1 yr and served as controls for the first group. In rats treated with EES and NEA, the liver wt increased markedly, while the body wt decreased. In the rats treated for 18 mo, the activities of glutamine oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase were higher and total cholesterol and triglyceride were lower, than those treated for only 1 yr. Multiple nodules ranging from 0.2 mm to 1 mm in diameter were observed in all the treated rats. These were hyperplastic nodules with compression and atrophy of the surrounding liver parenchyma. One of the 18 rats in the first group had a large, 2.5 x 2.0 x 1.5 cm, well-differentiated hepatocellular carcinoma composed of trabeculae of neoplastic cells. In rats treated for 18 mo, the number of hyperplastic nodules was higher and their size was larger than animals treated for 12 mo. These results support the hypothesis that EES and NEA may be initiators in hepatocarcinogenesis. (30 Refs)

37. EFFECT OF HYDROCORTISONE ON ACTIVITY OF ALPHA-GLYCEROPHOSPHATE DEHYDROGENASE IN KOCH-1 AND MOUSE GLIOBLASTOMA EPIT-5 CELLS.

Kondakova LI, Chudinovskaia NV, Brusovanik VI
Lab. Comparative Pathology, Inst. Human Morphology, Moscow, USSR
Arkh Anat Gistol Embriol; 80(5):86-90 1981

Activity of alpha-glycerophosphate dehydrogenase (a-GPD) was studied in mouse glioblastoma EPIT-5 (ependymoblastoma of immature type) and Koch-1 (adenovirus BA-3 induced connective tissue sarcoma) cell lines. aa-GPD activity in Koch-1 cells remained at a low level throughout the entire period of culturing; a-GPD activity in EPIT-5 cells reached the max on day 1-2 of culturing. Incubation of EPIT-5 cells with hydrocortisone resulted in an almost twofold increase of a-GPD activity. Hydroco rtisone did not affect a-GPD activity in Koch-1 cells. (26 Refs) (In RUS)

38. MEMBRANE SURFACE PROPERTIES OF NORMAL AND MALIGNANT CELLS: PARTITION IN AQUEOUS TWO-POLYMER PHASE SYSTEMS.

Sherbet GV, Lakshmi MS
Cancer Res. Unit, Univ. Dept. Clinical Biochemistry and Metabolic Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, England
Exp Cell Biol; 49(5):267-271 1981

The partition of normal and malignantly transformed fibroblast lines and cell lines initiated from malignant human astrocytomas and a benign ganglioneuroma has been examined in aqueous dextran-polyethylene glycol phase system containing phosphate buffer with a low phosphate/sodium chloride ratio. The malignant astrocytomas showed a significantly lower partition coefficient as compared with the benign ganglioneuroma. Treatment of astrocytoma cells with dexamethasone caused an increase in the partitioning of the cell population. No differences were found in the partition behavior of normal BHK-21 cells and their malignant transformants, the TRES fibrosarcoma cells. Polyoma and simian virus-transformed 3T3 fibroblasts showed partition ratios similar to the untransformed cells. Dexamethasone pre-treatment had no effect on the partition behavior of these cells. The significance of these observations has been discussed in relation to the surface hydrophobicity and the neoplastic site. (Author abstract) (11 Refs)

39. INHIBITION OF DNA SYNTHESIS IN MOUSE EPIDERMIS AND BREAST EPITHELIUM BY DEHYDROEPIANDROSTERONE AND RELATED STEROIDS.

Pashko LL, Schwartz AG, Abou-Gharbia M, Swern D
Fels Res. Inst., Temple Univ., Philadelphia, PA, 19140
Carcinogenesis; 2(8):717-721 1981

Male ICR mice and female virgin C3H-A/A mice were treated with dehydroepiandrosterone (DHEA), DHEA-sulfate, DHEA-sulfatide, 16alpha-Br-epiandrosterone (Br-Epi), estradiol-17beta, progesterone, testosterone, or corticosterone. The activity of glucose-6-phosphate dehydrogenase (G6PDH) and the level of incorporation of [3H]thymidine in male mouse epidermis was determined. Incorporation of [3H]thymidine was also measured in female mouse breast epithelium. DHEA and DHEA-sulfatide significantly inhibited G6PDH activity in the epidermis. DHEA-sulfate had no inhibitory effect. Br-Epi was the most active inhibitor of the steroids tested. DHEA and DHEA-sulfatide inhibited the stimulation of [3H]thymidine incorporation by 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse epidermis. DHEA-sulfate did not have this effect. Br-Epi was much more potent an inhibitor in both the epidermis and breast epithelium than DHEA. Of the sex steroids tested, only corticosterone inhibited TPA-stimulated incorporation of [3H]thymidine. The results indicate that the activity of DHEA, which has been shown to suppress spontaneous breast cancer development in mice, is not limited to breast epithelium. A possible relationship to spontaneous breast cancer in humans is suggested. (25 Refs)

40. INDUCTION AND FUNCTION OF 2',5'-OLIGOADENYLATE SYNTHETASE IN DIFFERENTIATION OF MOUSE MYELOID LEUKEMIA CELLS.

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Exp Cell Res; 135(1):191-197 1981

The activity of 2',5'-oligoadenylate synthetase (2-5A synthetase), known to be induced by interferon, was detected in mouse myeloid leukemic M1 cells only when they differentiated to phagocytic cells after incubation with conditioned medium (CM) from rat embryo cells. However, no interferon activity occurred in culture fluids of CM-treated M1 cells, although some activity was detected in the cell extracts. When anti-interferon serum was added to M1 cell cultures, the induction of 2-5A synthetase by CM was suppressed. These results suggest that CM stimulated the M1 cells to produce a minute amount of interferon, which was responsible for induction of the 2-5A synthetase activity. On the other hand, development of the phagocytic activity of M1 cells could not be influenced by addition of antiserum. Interferon added exogenously per se neither induced phagocytic activity of M1 cells, nor did it enhance the CM-induced differentiation of the cells. Moreover, dexamethasone, which induced differentiation of M1 cells, was not capable of inducing 2-5A synthetase. These results indicate that interferon and/or 2-5A synthetase plays no essential part in the differentiation of M1 cells. (Author abstract) (43 Refs)

41. THE EFFECTS OF ANDROGENS AND ESTROGENS ON HUMAN PROSTATIC CELLS IN CULTURE.

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Can J Physiol Pharmacol; 59(9):949-956 1981

A cell culture system has been developed in order to assess the response of human prostatic carcinoma cells to the presence of androgens and estrogens. A single cell suspension of these cells was incubated in minimum essential medium, in the absence of added sex steroids (standard culture), for 24 hr. Equal aliquots of these cultured cells were incubated for a further 24-72 hr in standard medium or in medium to which testosterone (T, 17.4 nM), dihydrotestosterone (DHT, 1.7 nM) or estradiol (E2, 0.36 nM) had been added. At the end of the incubations, the levels of tartrate-inhibitable acid phosphatase were compared in the standard cultures and the cultures to which sex steroids had been added. There were three patterns of response of patients' cells to the presence of androgens. From a total of 91 cell cultures, obtained from 85 patients, androgens were associated with an increased acid phosphatase production in 58. In 22 incubations, there was no androgenic effect on acid phosphatase production, and in 11 incubations, androgens were associated with lower enzyme levels than in the standard cultures. The qualitative effects of T and DHT were the same, but the quantitative effect of DHT was greater than that of T in those experiments in which there was a positive androgenic effect on acid phosphatase production. In 10 of 46 incubations with E2, acid phosphatase levels were lower than the standard incubations, while in 28 there was no difference in enzyme levels. In eight incubations, E2 was associated with a greater acid phosphatase production than that found in the standard cultures. In cultures of the cells from 180 men with benign prostatic hyperplasia and 5 men with normal prostatic tissue, androgens and estrogens had no effect on acid production by these cells, even at DHT concentrations of 1.7 x 10(-7) M. It is concluded that prostatic carcinoma cells behave differently, in culture, in response to sex steroids, than do cells from benign hyperplastic or normal prostatic tissue. (Author abstract) (15 Refs)

42. CHROMATIN ANALYSIS IN HUMAN ENDOMETRIAL ADENOCARCINOMA BEFORE AND AFTER TREATMENT WITH 6-METHYL-17-HYDROXYPROGESTERONE ACETATE (MPA).

Barni S, Novelli G, Zanoio L, Gerzeli G, Vecchietti G
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Virchows Arch [Cell Pathol]; 37(2):167-177 1981

Some molecular and ultrastructural characteristics of chromatin (propidium iodide intercalation into DNA during thermal denaturation. DNA content per nucleus and its hydrolysis kinetics, euheterochromatin ratio) were studied in the cells of endometrial adenocarcinomas following oral treatment with 6-methyl-17-hydroxyprogesterone acetate (MPA) at a dose of 1 g/day for 12 days. Ultrastructurally, before treatment the nuclei of tumor cells were often irregularly shaped and exhibited a mostly dispersed chromatin (euchromatin). In addition, the distribution of DNA content per cell was clearly abnormal, reaching ploidy levels of 16c. From a physicochemical standpoint, both the thermal denaturation and the HCl-hydrolysis of DNA revealed a high lability of chromatin. After progestin treatment, nuclear morphology appeared to approach normality, and large areas of heterochromatin reappeared which, after staining with propidium iodide, could be seen as strongly fluorescent points. DNA showed a higher resistance to thermal denaturation, especially evident at temperatures exceeding 70 C. Also the HCl-hydrolysis curves showed that, particularly with regard to short (less than 20 min) or protracted (greater than 140 min) hydrolysis times, DNA was less easily hydrolyzed than before MPA-treatment. A clearcut modification could be observed with regard to the DNA content per cell, high ploidy levels disappearing and values being less dispersed. On the whole, these findings demonstrated an effect of the drug on tumor cells, particularly affecting chromatin, at least with regard to the parameters examined. (Author abstract) (18 Refs)

43. PROSTATIC CANCER. I. 6-METHYLENE-4-PREGNEN-3-ONES AS IRREVERSIBLE INHIBITORS OF RAT PROSTATIC DELTAKETOSTEROID 5ALPHA-REDUCTASE.

Petrow V, Wang YS, Lack L, Sandberg A
Dept. Pharmacology, Duke Univ. Medical Center, Durham, NC, 27710
Steroids; 38(2):121-140 1981

Some derivatives of 6-methylene-4-pregnen-3-one were studied as inhibitors of delta-3-ketosteroid 5alpha-reductase. Max inhibitory activity was shown by 17-acetoxy-6-methylene-4-pregnene-3,20-dione (AMPD). Irreversible inactivation was observed following preincubation of the enzyme with NADPH and AMPD. This inactivation was found to occur only in the presence of NADPH. As such enzyme inactivation was not due to the formation of a more inhibitory metabolic product, or to the formation of a more inhibitory metabolic product, or to the formation of superoxide via a cytochrome P-450/NADPH pathway, it seemed likely that the observed inactivation was derived from an irreversible combination of the enzyme with AMPD. That this was probably the case was established by kinetic studies which revealed a pattern compatible with a k(cat) type of mechanisms. (Author abstract) (14 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

44. STUDY ON EFFECTIVENESS OF ESTRAMUSTINE PHOSPHATE DISODIUM (ESTRACYT) FOR CARCINOMA OF THE PROSTATE.

Okada K, Yamauchi T, Konami T, Yoshida O
Dept. Urology, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Hinyokika Kiyo; 27(5):565-575 1981

Effectiveness of Estracyt for carcinoma of the prostate was studied both clinically and experimentally. The drug was administered to 13 patients, 4 untreated and 9 relapsed cases from the previous endocrine manipulation. All of the former (100%) and 2 of the latter cases (22%), ie, 6 of 13 cases (46%) in total, responded well to this therapy. It may be postulated that effect Estracyt depends not only on estrogenic but also on cytotoxic activity as well, judged from marked degenerative figures on histological examination of the biopsy specimen, which has never been experienced through routine estrogen therapy. Although Estracyt did not show a significant reduction of the tumor size in nude mice, which had been obtained by injection of cultured cells established from a human prostatic cancer tissue, remarkable degeneration was observed on histological examination. (Author abstract) (15 Refs) (In JPN)

45. RESPONSE OF LYMPH NODE METASTASIS TO SEQUENTIAL ESTROGEN AND RADIATION THERAPY IN PROSTATE CARCINOMA.

Green N, Bodner H, Broth E, Garrett G, Goldberg H, Goldstein A, Polse S, Skaist L, Treible D, Wallack H
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Urology; 18(2):137-142 1981

Increasingly sophisticated diagnostic studies have shown a high incidence of tum or spread to the regional lymph nodes. The status of the lymph nodes has been evaluated by noninvasive diagnostic procedures such as lymphangiography and computerized axial tomography. The applicability of these procedures has been enhanced by the use of stringent criteria. Gross lymph node metastasis can be diagnosed with considerable confidence. Serial observations of lymphangiograms and computerized axial tomograms before and 2 mo after the administration of estrogens provide an added dimension to the interpretation of lymph node metastasis. The nature and range of the response of lymph node metastasis were observed. Survival of patients with gross lymph node metastasis treated by sequential estrogen and radiation therapy was evaluated. A total of 11/18 (61%) of patients remained free of symptoms, 8/11 (74%) with a favorable lymph node metastasis responsive to estrogen therapy, and 3/7 (42%) with lymph node metastasis refractory to estrogen therapy. Follow-up computerized axial tomograms of the lymph nodes done at 1 and 2 yr after irradiation showed a persistent favorable response. Five patients are alive with disease, and two patients died of the disease. (Author abstract) (25 Refs)

46. TREATMENT OF GRAFT-VERSUS-HOST DISEASE IN HUMAN ALLOGENEIC MARROW GRAFT RECIPIENTS: A RANDOMIZED TRIAL COMPARING ANTITHYMOCYTE GLOBULIN AND CORTICOSTEROIDS.

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Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Am J Hematol; 11(1):1-8 1981

This prospective randomized trial compared the effect of antihuman thymocyte globulin (ATG) vs corticosteroids as treatment of graft-vs-host disease (GVHD) in recipients of HLA-identical allogeneic bone marrow transplants. Patients undergoing transplantation as therapy for either hematologic malignancies or aplastic anemia were given methotrexate as postgrafting immunosuppression. Patients who nevertheless developed acute GVHD of moderate severity were randomized to receive either corticosteroid therapy or ATG therapy. Thirty-seven patients were randomized: 20 patients received corticosteroids, and 17 received ATG. Both ATG and corticosteroids were in general well tolerated, although all patients receiving ATG developed fever and chills. Both treatment modalities were associated with a mild decrease in severity of GVHD after therapy. There was, however, no significant difference between treatment groups, whether assessed by improvement in specific organ involvement, improvement in the overall grade of GVHD, need for additional therapy for acute GVHD, or the proportion of patients who developed chronic GVHD. Infectious complications and survival were also not different between treatment groups. Thus, corticosteroids were as effective as ATG for the treatment of acute GVHD in recipients of HLA-identical marrow transplant s and, therefore, appear to be a reasonable choice as primary therapy for acute GVHD. (Author abstract) (21 Refs)

47. CORTICOSTEROIDS FOR ELDERLY PATIENTS WITH BREAST CANCER.

Minton MJ, Knight RK, Rubens RD, Hayward JL
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Cancer; 48(4):883-887 1981

Ninety-one assessable elderly women (greater than or equal to 65 yr) with advanced breast cancer were treated with prednisolone 15 mg (or cortisone 75 mg) daily afte primary endocrine treatment (estrogens, androgens or tamoxifen). Thirteen (14%) achieved an objective regression, and 19 (21%) others showed no change for greater than or equal to 6 mo. Hence, 32 patients (35%) had control of disease for about 1 yr. Responses were mainly in soft tissue and skeletal lesions and were independent of response to prior endocrine treatment. Toxicity was low. Low-dose corticosteroid treatment is of value in controlling advanced breast cancer in elderly women. (Author abstract) (28 Refs)

48. STEROID RESPONSIVENESS OF THE HUMAN CELL LINE NHIK 3025.

Ostgaard K, Wibe E, Eik-Nes KB
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Acta Endocrinol (Kbh); 97(4):551-558 1981

The human cell line NHIK 3025, derived from a carcinoma of the uterine cervix, contains a glucocorticoid and an androgen receptor. The effect of various natural and synthetic steroid hormones and antihormones on growth rate of these cells was therefore investigated. Cells grown in Eagle's MEM with 10% fetal calf serum exhibited reduced growth when cultured with dexamethasone due to prolongation of the cell cycle. Glucocorticoid anti-inducers like progesterone had no significant effect on cell growth. Methyltrienolone (R 1881) or 5alpha-dihydrotestosterone did not affect cell proliferation. The reported shortening of the cell cycle by testosterone is probably not directly connected with activation of the androgen receptor present, but possibly dependent on metabolic conversion of testosterone to the more potent growth stimulator 4-androstene-3beta,17beta-diol. The effect of several anti-androgens was also studied. The non-steroidal anti-androgens flutamide and SCH 16483 had no significant effect on cell proliferation. It was, however, found that a number of steroid anti-androgens, including R 2956, stimulated cell growth. A significant stimulatory effect by R 2956 was seen within the first cell generation, 4-androstene-3beta,17beta-diol had to be present during 2 days, and testosterone for even longer times before a similar effect on cell growth could be obtained. (Author abstract) (24 Refs)

49. EFFECTS OF HEXESTROL, MEDROXYPROGESTERONE ACETATE AND CHLORMADINONE ACETATE ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY CANCER IN RELATION TO ESTROGEN RECEPTOR.

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Gan; 72(4):604-609 1981

The effects of hexestrol (HXS), medroxyprogesterone acetate (MAP) and chlormadinone acetate (CMA) on 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats were evaluated. As a result of successive im injections of HXS at dosages of 2 or 10 mg/kg or MAP at dosages of 24 or 120 mg/kg, tumors were markedly reduced in size in all groups on day 7-day 14. These effects were the same regardless of the presence or absence of cytoplasmic estrogen receptors (ER) in tumors as determined by the dextran-coated charcoal method. Although such an effect was also seen with CMA, it was much less marked than the effects seen with HXS and MAP. The body wt of HXS-administered groups decreased considerably, whereas those of MAP-administered groups increased. These results may suggest that there is another endocrinological tumor-suppressing mechanism besides the mechanism involving the estrogen-ER system in large-dose administration of HXS and MAP. (Author abstract) (13 Refs)

50. RESISTANCE TO ANDROGEN IN MURINE LYMPHOSARCOMA LINES RESISTANT OR SENSITIVE TO GLUCOCORTICOID HORMONE.

Sasson S, Mayer M
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Br J Cancer; 44(1):127-128 1981

The effects of dexamethasone (DX: 1 mg/mouse) and nandrolone phenproprionate (NP: 2.5 mg/mouse) on CDF male mice implanted with glucocorticoid-sensitive and -resistant strains of lymphosarcoma P-1798 were determined. Treatment with NP failed to affect the wet wt, the dry wt, or the DNA/protein ratio of either the glucocorticoid-sensitive or -resistant tumor lines. In contrast, DX produced the expected involution of the glucocorticoid-sensitive line. The regression of the tumor induced by DX seemed to reflect cell lysis rather than loss of cellular water or protein, since the dry wt and the DNA/protein ratio remained almost unchanged. The glucocorticoid-resistant line did not respond to DX. DX caused a marked reduction, 41% and 71% of thymus wet wt, in mice bearing the glucocorticoid-sensitive and -resistant tumors, respectively. By contrast, NP caused 61% and 62% reductions, respectively. (5 Refs)

51. BREAST CANCER INCIDENCE IN WOMEN WITH A HISTORY OF PROGESTERONE DEFICIENCY.

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Am J Epidemiol; 114(2):209-217 1981

In order to investigate the nature of the association of involuntarily delayed first birth and risk of breast cancer, 1,083 white women who had been evaluated and treated for infertility from 1945-1965 were followed prospectively through April 1978 to ascertain their breast cancer incidence. These women were categorized as to the cause of infertility into two groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4x the risk of premenopausal breast cancer compared to women in the NH group. This excess risk could not be explained by differences between the two groups in ages at menarche or menopause, history of oral contraceptive use, history of benign breast disease or age at first birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups. (Author abstract) (23 Refs)

52. PROTECTIVE EFFECT OF ORAL CONTRACEPTIVES AGAINST CANCER OF THE REPRODUCTIVE ORGANS.

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Lakartidningen; 78(28/29):2591-2592 1981

Studies on the protective effect of oral contraceptives, especially combined contraceptives, against cancer in the reproductive organs are reviewed. The combined oral contraceptives are more or less gestagen-dominated. They can therefore be expected to reduce the frequency of estrogen-dependent tumors. There is no clear evidence of a reduced incidence of breast cancer among women using such combined oral contraceptives: most studies show no change in the frequency of breast cancer, but one study showed reduced breast cancer risk in the age group 31-40 yr, and increased breast cancer risk in women who continued taking oral contraceptives beyond the age of 45 yr. Some studies showed a lower growth and later metastasized breast cancer in women who had used oral contraceptives compared with women who had not used contraceptives. The epidemiological studies show a marked reduction of the frequency of ovarian and endometrial cancer in women who had used oral contraceptives to half to one third of the frequency in women who had not used oral contraceptives. (12 Refs) (In SWE)

53. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

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Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (28 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

54. LONG-TERM EFFECTS OF PERINATAL EXPOSURE TO 5ALPHA-DIHYDROTESTOSTERONE ON NORMAL AND NEOPLASTIC MAMMARY DEVELOPMENT IN MICE.

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Endocrinol Jpn; 28(2):231-234 1981

Previous published observations of the effects of neonatal treatment with various aromatizable and nonaromatizable androgens and with 5beta-dihydrotestosterone (5b-DHT) in particular prompted this study of prenatal and neonatal treatment with 5alpha-dihydrotestosterone (5a-DHT) on mammary and pituitary growth and function. Pregnant SHN mice (a high mammary tumor strain) were given daily sc injections of 1 mg 5a-DHT dissolved in 0.1 ml olive oil 4 x on days 12-15 of pregnancy (prenatal treatment; 22 mice). Newborn mice from untreated mothers received 200 ug 5a-DHT/day sc in 0.02 ml olive oil 5 x on days 1-5 after birth (neonatal treatment; 30 mice). On the afternoon of estrous at 4 mo of age, five mice from each group were bled and sacrificed for laboratory examination; the remaining mice were followed until 9 mo of age for tumor development. No effect of treatment on body wt was seen in any group. Neonatal treatment with 5a-DHT resulted in significantly higher anterior pituitary wt and lower adrenal and ovarian wt than in the controls, and histological appearance of the ovaries was abnormal; prenatal treatment did not have these effects. Neonatal treatment resulted in a significantly higher incidence of mammary tumors at 5, 6, 7 and 9 mo of age (p less than 0.01-0.02), with final tumor incidences of 25/25 and 13/17 in the neonatal and prenatal treatment groups, respectively. The mice treated neonatally had significantly higher plasma prolactin level (199 +-13 nanog/ml) than did controls (51 +-9 nanog/ml), but pituitary prolactin content and concentration were similar; prenatal treatment did not affect these parameters. These results indicate that the long-term effects of perinatal treatment with 5b-DHT on normal and neoplastic mammary growth and pituitary prolactin secretion are much more marked than are the effects of 5a-DHT treatment. (8 Refs)

55. INFLUENCE OF THE ESTROUS CYCLE DURING CARCINOGEN EXPOSURE ON NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMA.

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Cancer Res; 41(10):3857-3862 1981

The influence of individual stages of the rat estrous cycle during exposure to 1-nitroso-1-methylurea (NMU) on mammary tumor incidence, latency, number, and cytosol receptor dynamics for estrogen and progesterone was determined. Virgin female Buffalo rats were separated into three groups on day 53 according to their vaginal smear pattern. NMU (5 mg/100 g body wt, iv) was administered in 3 mo doses beginning at 53 to 55 days of age on diestrus, proestrus, or estrus between 9:00 and 11:00 a.m. Groups of rats had their second and third injections of NMU on the same day of the estrous cycle as their initial injection. All animals were killed during the morning on a diestrus day. Receptors for estrogen and progesterone were determined by a modified dextran-coated charcoal method and by sucrose density gradient analysis. Mean latencies to first tumor appearance in diestrus, proestrus, and estrus groups were 104.4, 83.6, and 91.4 days, respectively (p less than 0.05, diestrus versus estrus and proestrus) following the NMU injection. The mean number of tumors per rat was significantly higher in rats injected on proestrus (4.5) or estrus (4.3) than on diestrus (2.0). Estradiol bound to receptor sedimented at 8 and 4 s and was suppressed by diethylstilbestrol and estradiol. Progesterone receptor migrated to 7.8 and 4 s regions. Estrogen receptor incidence (100%) and content (16.7 fmol/mg cytosol protein) was highest in rats injected on diestrus. In the proestrus and estrus injected groups, estrogen receptor incidence was 95 and 63% and content was 10.2 and 11.2 fmol/mg protein, respectively. The affinity of estradiol for its receptor was not significantly altered in any group. Although there were no statistically significant differences in progesterone receptor incidence or affinity between groups, progesterone receptor content (74.6 fmol/mg cytosol protein) was significantly higher in tumors from rats injected on proestrus than on diestrus. These data suggest that the prevailing hormonal milieu of the estrous cycle during NMU exposure may be critically important to the subsequent biological behavior and steroid receptor status of carcinogen-induced rat mammary tumors. (Author abstract) (41 Refs)

56. ANTIANDROGEN EFFECTS ON ANDROGEN-RESPONSIVE MAMMARY TUMOUR CELLS IN CULTURE.

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J Steroid Biochem; 14(9):819-822 1981

The effects of flutamide (FL), hydroxyflutamide (HFL), and cyproterone acetate (CP) on the growth of androgen-responsive mouse mammary tumor cells was investigated because such antiandrogens have clinical cancer chemotherapy applications, although they can cause unwanted side-effects. In the presence of 35 nanoM testosterone, the cell growth rate but not the final cell density was inhibited by 100-fold excesses of each of the tested drugs, HFL and CP being more effective than FL. When tested over a wide range of doses (approx 2 x 10(-10) to approx 5 x 10(-5)) in a short-term growth assay, HFL and CP were more effective than FL in terms of overall inhibition and they were active at 100-fold lower concentrations than FL. The binding of the androgen 5alpha-dihydrotestosterone (DHT) to the cytoplasmic androgen receptor was inhibited by HFL and CP but not by FL. The growth inhibitory activities of HFL and CP are probably related to their ability to inhibit androgen binding to the cytoplasmic androgen receptor, but the effects of FL are not readily interpreted from these findings. (12 Refs)

57. EFFECT OF OVARIECTOMY ON SERIALLY TRANSPLANTED RAT MAMMARY TUMORS INDUCED BY 7,12-DIMETHYLBENZ[A]ANTHRACENE.

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Eur J Cancer Clin Oncol; 17(7):801-808 1981

Mammary tumors in inbred Fischer 344 female rats were induced by 7,12-dimethylbenz[a]anthracene (DMBA). Primary tumors were excised and transplanted sc to syngeneic recipients. The transplanted tumors, thus developed, were used for further serial transplantation of up to five passages. Transplanted Tumors were able to grow to 1.5-2 cm in diameter within 1-2 mo. Histologically, tumor tissues of early passages were characterized by mixed populations of epithelial and spindle cells while tumors of late passages contained only the spindle cells. Tumors grafted into ovariectomized hosts were not able to grow, although they remained viable, since estrogen therapy was able to activate their growth. By the third passage, tumors were able to grow when transplanted into ovariectomized recipients but the growth rate was considerably slower than that in the intact hosts. In the fourth and fifth passages, tumors transplanted in ovariectomized recipients grew as well as those in intact hosts. Following the establishment of the transplanted tumors, ovariectomy in the hosts resulted in an initial regression and subsequent regrowth of tumors of early passages and had no effect on those of late passages. The long-term growth of tr ansplanted tumors in ovariectomized hosts was associated with an increase in the spindle cell population which gradually replaced the regressed epithelial cells. Results suggest that the so-called 'hormone-dependent' DMBA-induced mammary tumors consist of at least two histologically and biochemically distinct cell types, hormone-dependent epithelial and hormone-independent spindle-shaped cells, and that the latter are selected over the epithelial component during serial transplantations or under unfavorable hormonal conditions due to ovariectomy in the hosts. (26 Refs)

GENERAL REVIEWS ON STEROID HORMONES

58. WHAT ARE WE WAITING FOR IN CHEMOTHERAPY IN UROLOGY?.

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Sem Hop Paris; 57(25/26):1228-1237 1981

The use of chemotherapeutic agents in the treatment of urological neoplasms is reviewed. The value of chemotherapy has been proven in the treatment of testicular and Wilms' tumors and pelvic rhabdomyosarcomas. In the bladder cancer treatment intravesicular [adriamycin (ADR), bleomycin (BLM), and 5-fluorouracil (5-FU), thiotepa and etoglucide], and systemic mono- [cyclophosphamide (CP), ADR, cis-platinum (CPT), 5-FU, methotrexate (MTX), and BLM] and polychemotherapy (ADR and CP, CP and CPT, ADR and 5-FU, and CP, 5-FU, and ADR) is considered. Other treatments for bladder cancer, such as local-regional chemotherapy and immunotherapy, are considered. The results of mono- (5-FU, hydroxyurea, and CPT) and polychemotherapy are compared with other regimens, including estrogens, antiandrogens, antiestrogens, hypophysectomy, immunotherapy, castration, radiotherapy, and radioactive phosphate, for the treatment of prostatic neoplasms. Although renal adenocarcinomas are considered resistant to chemotherapy, antineoplastic agents may be of use in decreasing the possibility of metastasis. Regimens suggested for this purpose include mono- (lomustine and vinblastine) and polychemotherapy (lomustine plus vinblastine or VM 26), ia chemotherapy, hormone therapy (medroxyprogesterone acetate), and immunotherapy. (155 Refs) (In FRE)

59. POSSIBILITIES AND PROBLEMS OF ORGAN-SELECTIVE AGENTS AND DRUGS.

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Pharmazie; 36(6):391-399 1981

The development of organ-selective methods of treatment are reviewed, and several specific types of treatment are described. Localized therapy involves the introduction of an agent into the site to be treated. An example of this is the progesterone intrauterine contraceptive system. A second method relies on the differences between metabolic processes in normal and malignant cells. Compounds such as cyclophosphamides are used to selectively poison tumor cells. Acid-stimulating compounds can lower the pH of tumor cells, allowing cytotoxic agent active at lower pH to be effective. Liposomes, in which water-soluble compounds are enveloped in lipid double-layers, enable the transport of agents selectively into target cells. Micelles work in a similar manner. Certain radioactive elements have been shown to accumulate selectively in certain organs, such as 131I in the thyroid. This has provided diagnostic and therapeutic tools, useful particularly in malignant diseases. The combining of isotopes with specific carrier compounds allows the specific targeting of organs or tissues. Hormones with specific organ affinities, as well as specific hormone receptors, can also be used to direct cytotoxic agents at specific targets. The development of organ-specific treatments has many possibilities for treatment of cancer and other diseases. (52 Refs) (In GER)

60. HORMONES: NEW POTENTIAL FOR TUMOR MARKERS.

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Diagn Med; 4(4):59-60,62,64-66,68,72,74 1981

Very useful diagnostic tests exist for functional tumors of the endocrine glands that measure the abnormal hormonal secretions. Medullary carcinoma of the thyroid is derived from the calcitonin-producing C-cells and secretes excessive amounts of calcitonin; a provocative test for calcitonin secretion coupled with serum calcitonin measurements is useful in screening and diagnosis. Pheochromocytomas are best detected by tests for urinary excretion of catecholamines or their metabolites. Carcinoid tumors, which arise from enterochromaffin cells in many areas of the body, actively produce vasoactive peptides such as serotonin, histamine, and kallikrein and secrete biogenic amines; the most useful test for them is measurement of the urinary 5-hydroxyindoleacetic acid. Islet cell tumors may be associated with the overproduction of numerous hormones, including insulin, glucagon, gastrin, and somatostatin, and numerous tests exist to measure these abnormalities. Adrenocortical carcinomas may secrete excessive amounts of glucocorticoids, mineralocorticoids, androgens, or estrogens, all of which may be measured directly or indirectly (by their metabolites) in serum and/or urine. Testicular tumors may be germ-cell tumors that secrete chorionic gonadotropin or Leydig-cell tumors that secrete estrogens or androgens; they may also be accompanied by elevated levels of alpha-fetoprotein; all of these substances are amenable to assay. Most ovarian tumors do not secrete abnormal amounts of hormones, but may overproduce estrogens, androgens, and progestogens. Ectopic production of virtually every protein or polypeptide hormone is common but extremely variable so that tests for such production are not very cost-effective as screening procedures, although serial hormone measurements in these cases can be useful as a clinical monitor. (24 Refs)

61. BREAST CANCER, PREGNANCY, AND THE PILL.

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Br Med J; 283(6294):778-779 1981

Roles of parity and oral contraceptive use in the etiology of breast cancer are discussed. Clear histological and physiological changes are observed in the breast following pregnancy. A decrease in number of clear cells and an altered response to hormones is seen after a single pregnancy. Cyclic DNA and IgA synthesis are found only in parous women. Plasma concentrations of estrogen and progesterone are similar in both parous and nulliparous women, but pregnancy permanently alters the hormonal responsiveness of breast epithelium. The carcinogenic effect of estrogen unopposed by progesterone on the breast is hypothesized. Prior to pregnancy a woman has an inadequate number of endogenous progesterone receptors so that even with a combined estrogen-progesterone contraceptive pill, breast tissue may in effect experience 'unopposed' estrogen. Nulliparity and delayed first pregnancy may be important risk factors for subsequent breast cancer. Future study should focus not on hormonal profile but on effects of hormones on the breast itself. (24 Refs)

62. CURRENT STATUS OF THERAPEUTIC MODALITIES FOR TREATMENT OF GYNECOLOGIC MALIGNANCIES WITH EMPHASIS ON CHEMOTHERAPY.

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Am J Obstet Gynecol; 141(1):81-98 1981

The current status of conventional therapies for gynecological malignancies is reviewed with special emphasis on the efficacy of chemotherapy. Detailed discussions are presented on the prognostic factors, surgical management, radiotherapy, chemotherapy, along with recommendations relative to ovarian cancer (including malignant germ cells tumors), carcinoma of the cervix, endometrial cancer and gestational trophoblastic disease. Radiotherapy in combination with surgery is the treatment of choice for malignant germ cell tumors of the ovary, carcinoma of the cervix, and low-risk Stage I endometrial cancer. The patients with advanced ovarian cancer, advanced carcinoma of the cervix who have para-aortic node metastases, advanced endometrial cancer, and uterine sarcoma who have an extrapelvic extension of the disease, high-grade histology, or metastases would benefit from aggressive postsurgical systemic therapy. Chemotherapy regimens containing bleomycin and mitomycin C were found to improve the survival of the patients with advanced cervical cancer. Progestational agents were used widely in the treatment of endometrial cancer: the efficacy of hormonal therapy was found to depend upon the progesterone affinity of the tumor. Drug regimens containing adriamycin and dacarbazine were the most effective in the patients with soft tissue uterine sarcomas. (199 Refs)

OTHER RELATED STUDIES

63. ENDOCRINE MANIFESTATIONS OF CANCER AND ITS TREATMENT.

Shalet SM

Christie Hosp., Manchester, England

Practitioner; 225(1356):829,831,833,835,836 1981

Endocrine manifestations of cancer may be due to ectopic secretion in non-endocrine tissue and also may be due to secretion of a 'foreign' hormone from a tumor of an endocrine gland. Syndromes resulting from ectopic hormone secretion of various tumors and the appropriate treatments are discussed. Presented are ectopic ACTH secretion, ectopic anti-diuretic hormone production, disturbances resulting in hypercalcemia, ectopic human chorionic gonadotropin secretion, calcitonin production, erythrocytosis associated with malignant disease, and implications of such ectopic hormone secretion. A second section outlines the endocrine consequences of the treatment of cancer. It is now known that hypopituitarism may be caused by external radiation not directly involving the hypothalamic-pituitary region. Deficiency of thyrotropin, ACTH and gonadotropins may also result from radiation to the hypothalamic-pituitary axis. Radiation-induced dysfunction of the thyroid has been related to therapeutic radiation for various conditions. An increased incidence of hyperparathyroidism has been reported in patients with previous irradiation of the neck. Gonadal function in both male and female may be induced by radiation and cytotoxic agents. (6 Refs)

64. TREATMENT OF THE PATIENTS WITH CANCER OF THE PROSTATE.

Kan DV, Dunaevskii IaL
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Urol Nefrol (Mosk); (4):29-34 1981

The results of treatment of 98 patients (aged 53 to 82 yr) with cancer of the prostate are reported. There were 6 patients with Stage I, 83 with Stage II-III, and 9 with Stage IV. Diagnosis was confirmed histologically in 92 patients; 6 were found to have bone metastases. Ninety-five patients received continuous hormonal therapy. Treatment consisted of initial induction therapy with large doses of estrogens, followed by maintenance therapy with small doses. The optimal estrogen level (500-1,500 epithelial cells in 1 ml of urine sediment) was achieved in 93.1% of the patients. Orchiectomy was performed in 13 patients with resistance or intolerance to estrogens. The 5-yr survival rate in the patients subjected to estrogen therapy was 64.5%. (23 Refs) (In RUS)

65. INFLUENCE OF CONJUGATED OESTROGENS ON CIRCULATING OESTRADIOL, OESTRONE, LH, FSH AND PROLACTIN LEVELS IN POSTMENOPAUSAL WOMEN.

Luisi M, Franchi F, Argenio GF, Barletta D, Romano MR, Bernini GP, Gasperi M, Sgrilli R
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Int J Tissue React; 3(2):77-81 1981

The effect of a conjugated estrogen (Equormon-ION, obtained from pregnant mares' urine; 1.5 mg/day for 20 consecutive days po) on plasma 17-beta-estradiol (E2), estrone (E1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL) levels was studied in six 60-68-yr-old menopausal women. The time elapsed from surgical or spontaneous menopause was 6-12 yr. The plasma E1 level increased significantly from 28 picog/ml before treatment to 108 picog/ml after 20 days of treatment (p less than 0.001). Five days after the last dose of the conjugated estrogen, the mean plasma levels of both steroids were similar to the control values. The mean plasma levels of LH and FSH decreased progressively and significantly from 114 and 105 milli units (mU)/ml, respectively, before treatment to 43 and 36 mU/ml, respectively (p less than 0.001). Both the LH and FSH levels were significantly higher 5 days after the estrogen treatment than at its end (p less than 0.001). The conjugated estrogen treatment has no significant effect on the pattern of pituitary PRL secretion. The preliminary results seem to indicate that the possible effects of elevated plasma prolactin levels, usually observed during long-term estrogen treatment in menopausal women, on the development and growth of breast cancer, could be avoided. (16 Refs)

66. ECTOPIC ADRENOCORTICOTROPHIC (ACTH) SYNDROME AND SMALL CELL CARCINOMA OF THE LUNG--ASSESSMENT OF CLINICAL IMPLICATIONS IN PATIENTS ON COMBINATION CHEMOTHERAPY.

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Cancer; 48(5):1082-1087 1981

Small cell carcinoma of the lung is the tumor most commonly associated with ectopic ACTH production and hypercortisolism. The relationship between this paraneoplastic endocrine syndrome and the clinical course of the tumor is examined in this review of patients with the ectopic ACTH syndrome and small cell carcinoma seen at The Johns Hopkins Oncology Center between 1973 and 1979. Five of 157 (3.2%) patients with small cell carcinoma were clinically diagnosed as having the ectopic ACTH syndrome. The onset of this endocrine syndrome appeared to coincide with a more aggressive phase of the course of small cell carcinoma. Further analysis of these cases suggests that the development of the ectopic ACTH syndrome may reflect changes in cell populations within the tumor and/or alterations in tumor behavior with time and perhaps with the effects of drug therapy. (Author abstract) (20 Refs)

67. OSTEONECROSIS IN PATIENTS WITH MALIGNANT LYMPHOMA: A REVIEW OF TWENTY-FIVE CASES.

Engel IA, Straus DJ, Lacher M, Lane J, Smith J
Dept. Radiology, Memorial Sloan-Kettering Cancer Center, 1375 York Ave., New York, NY, 10021
Cancer; 48(5):1245-1250 1981

A retrospective study of 25 patients with malignant lymphoma who had osteonecrosis of either the femoral or humeral head(s) was undertaken. The common factor present among all patients was the administration of intermittent steroid-containing combination chemotherapy. Seventeen Hodgkin's disease patients received chemotherapy predominantly consisting of an alkylating agent, vincristine, procarbazine, and moderate amounts of prednisone. The non-Hodgkin's lymphoma patients were on various moderate dosage steroid-containing protocols, except three who received prolonged high-dose steroid-containing chemotherapy regimens. Sixteen of the 17 Hodgkin's disease patients and five of the eight non-Hodgkin's lymphoma patients received radiotherapy to the bones that subsequently developed osteonecrosis. Two of the three non-Hodgkin's lymphoma patients who were not irradiated were treated with high-dose steroid-containing chemotherapy regimens. Symptoms developed in patients 12 mo and 32 mo after completion of chemotherapy and radiotherapy, respectively. Osteonecrosis was a long-term complication of treatment between 1970 and 1979 and occurred in 1.6% of the Hodgkin's disease and 0.12% of the non-Hodgkin's lymphoma patients treated. The authors conclude that the patients at highest risk for this complication are those who receive both radiotherapy to the affected bone(s) and intermittent steroid-containing multiple drug chemotherapy. (Author abstract) (24 Refs)

68. LESS TOXIC TREATMENT FOR ADVANCED BREAST CANCER.

Henderson IC
Sidney Farber Cancer Inst., Boston, MA, 02115
N Engl J Med; 305(10):575-577 1981

Placed within the context of the variety of endocrine manipulations long used effectively to treat patients with metastatic breast cancer is the relatively new endocrine therapy, aminoglutethimide. The drug has been found to be safe, effective, and minimally toxic when compared with most other anticancer therapies. After its administration a fall in circulating estrogens similar to that seen after adrenalectomy is seen. This fall has been shown to result from inhibition of conversion of androstenedione to estrone in non-adrenal tissues. Tumor regression in some patients not responding to surgical adrenalectomy has also been observed after aminoglutethimide therapy. These results, together with relatively low toxicity and reversibility of action, make the drug a reasonable second therapy after tamoxifen in postmenopausal women and worthy of inclusion among effective treatments for breast cancer. (14 Refs)

69. CHANGES IN TYROSINE LEVELS OF BLACK AND WHITE SKINS OF GUINEAPIGS TREATED WITH PSORALEN AND HORMONES.

Mondal M, Banerjee PK
Dept. Physiology, Univ. Coll. Medicine, Calcutta Univ., Calcutta 700 009, India
Indian J Exp Biol; 19(2):189-190 1981

Adult guinea pigs of each sex received no treatment, 1 mg psoralen, 0.24 mg testosterone propionate injected ip in males every other day for 5 days, 7.5 mg hydrocortisone ip, 2 ug estradiol/female/day for 14 days, or 4 mg estradiol/female/day for 14 days. Administration of psoralen increased the tyrosine content of both white and black skins, with higher concentrations in white skin than black. Hydrocortisone increased the tyrosine content in white skin, but did not affect black skin. Testosterone propionate and estradiol both decreased tyrosine in white and black skin. This decrease may be due to increased incorporation of the amino acid into protein. (16 Refs)

70. EFFECTS OF VALPROIC ACID, NALOXONE AND HYDROCORTISONE IN NELSON'S SYNDROME AND CUSHING'S DISEASE.

Elias AN, Gwinup G, Valenta LJ
Div. Endocrinology, UCI Medical Center, 101 City Drive South, Orange, CA, 92668
Clin Endocrinol (Oxf); 15(2):151-154 1981

Two patients with Nelson's syndrome and one patient after bilateral adrenalectomy for Cushing's disease, without any evidence of Nelson's syndrome, were studied with respect to the effect of hydrocortisone, naloxone and valproic acid (a GABA transaminase inhibitor) on ACTH secretion. Hydrocortisone suppressed plasma ACTH concentrations to normal in the patient without Nelson's syndrome, but failed to do so in the two patients with Nelson's syndrome. Naloxone and valproic acid caused a decline in plasma ACTH concentrations in the patients with Nelson's syndrome, but produced no change in the patient without Nelson's syndrome. Secretion of ACTH may thus be influenced by both opiate peptides and by gamma aminobutyric acid, as well as by the cortisol concentrations, these agents may act a different sites to inhibit ACTH release by the tumor. (Author abstract) (14 Refs)

71. VISUALIZATION BY LIGHT AND SCANNING ELECTRON MICROSCOPY OF REPRODUCTIVE TRACT LESIONS IN FEMALE MICE TREATED TRANSPLACENTALLY WITH DIETHYLSTILBESTROL.

Lamb JC, Newbold RR, McLachlan JA
Natl. Toxicology Program, P. O. Box 12233, Research Triangle Park, NC, 27709
Cancer Res; 41(10):4057-4062 1981

Pregnant female mice were exposed to diethylstilbestrol or 11beta-methoxy-17beta-estradiol on days 9 to 16 of gestation. The female offspring of these animals were then examined for reproductive tract abnormalities. Scanning electron microscopic and histological evaluation of these specimens demonstrated reproductive tract lesions in all treatment groups when compared to matched control mice. These lesions included displacement of the squamocolumnar junction, uterine squamous metaplasia, atypical uterine cell surface specializations, protrusions of uterine cells, vaginal and cervical papillary growths, enlarged uterine cervix, abnormal vaginal and uterine folding patterns, female hypospadias, and the presence of vaginal concretions. Scanning electron microscopic observations proved particularly useful in studying lesions which involved the disruption of the normal structure and shape of the reproductive tract and the displacement of cell types. (Author abstract) (22 Refs)

72. EFFECTS OF LECTINS ON CAMP PRODUCTION AND STEROIDOGENESIS IN CULTURED ADRENAL TUMOR CELLS.

Lifrak E, Chen CC, Wishnow RM
Veterans Admin. Medical Center, Long Beach, CA, 90822
Exp Cell Res; 135(1):167-177 1981

The plant lectins, concanavalin A (conA), wheat germ agglutinin (WGA), and phytohemagglutinin (PHA) stimulate steroidogenesis in cultured adrenal tumor cells. ConA max stimulated steroidogenesis at 100 ug/ml following an approx 4 hr lag phase. ConA stimulation was completely inhibited by alpha-methyl-D-mannopyranoside and the WGA effect was prevented by N-acetyl-D-glucosamine. It was also found that conA alone did not cause a measurable increase in either intra- or extracellular cyclic AMP (cAMP) production. In addition, conA when added simultaneously with ACTH doubled the intra- and extracellular cAMP production over controls treated with ACTH alone. This enhancement effect was dose dependent. When Y-1 cells were preincubated with conA and then treated with either ACTH or cholera enterotoxin (CT) there was a dose- and time-dependent inhibition of induced cAMP production. In the case of CT, the inhibitory effect occurred even with simultaneous addition of conA and CT. This effect was reversed by addition of both alpha-methyl-D-mannopyranoside and washing with Eagle's minimal essential medium (MEM) 1 hr after CT had bound to its receptor. This reversal was not apparent for the inhibitory effect of conA on ACTH-induced cAMP production which occurred after 2 h of preincubation with conA. These results demonstrate that conA, as well as the other plant lectins, interact with specific membrane receptors to reversibly stimulate steroid production as well as enhancing or inhibiting ligand-induced cAMP production in cultured adrenal tumor cells. (Author abstract) (38 Refs)

73. POSTMENOPAUSAL BONE MINERAL LOSS AFTER TREATMENT FOR MALIGNANT GYNAECOLOGIC TUMOURS.

Lamke B, Bjorkholm E
Dept. Medical Engineering, Karolinska Institutet, P.O. Box 60400, S-104 01 Stockholm, Sweden
Acta Radiol Oncol Radiat Phys Biol; 20(2):109-111 1981

Bone mineral content after treatment for malignant gynecologic tumors was examined in women of fertile age. The treatment given was intracavitary radium applications followed by bilateral oophorectomy. In women who received estrogen substitution the bone mineral content increased by 1% a yr, whereas nonsubstituted women lost 3% of their initial bone mineral content per yr. The findings suggest that estrogen deficiency is the predominant cause of bone mineral loss initiated by this therapy. (Author abstract) (7 Refs)

74. HISTOPATHOLOGIC DISTINCTIONS IN THE RELATIONSHIP OF ESTROGENS AND ENDOMETRIAL CANCER.

Horwitz RI, Feinstein AR, Vidone RA, Sommers SC, Robboy SJ
Robert Wood Johnson Clinical Scholar Program, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT, 06510
JAMA; 246(13):1425-1427 1981

The slides of 233 patients included in a case-control study of estrogens and endometrial cancer were reviewed to determine how often endometrial cancer was misdiagnosed and whether patients with uterine cancer had other coexistent endometrial diseases. Reasonably close agreements were found among the original diagnoses and those of three additional reviewers (the total range of disagreements among all pathologists was from 2% to 16%). Proliferative and hyperplastic endometrium coexisted in many specimens from patients with endometrial cancer, and especially in those who had used estrogen replacement therapy. In contrast, estrogen therapy had seldom been used by patients whose cancers were not accompanied by these proliferative and hyperplastic lesions. In addition, these changes were found significantly more often in women with Grade 1 cancers than Grade 2 or 3 cancers. We conclude from these data that diagnostic misclassification is uncommon and that coexistent proliferative and hyperplastic lesions occur frequently, especially among women with Grade 1 cancers. The data also suggest that the frequent finding of Grade 1 cancer in estrogen users is due to bleeding that results from the stimulated coexistent benign proliferating endometrium. (Author abstract) (12 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

STEROID HORMONE SYNTHESIS AND METABOLISM

1. ESTROGENIC EFFECTS OF PHYSIOLOGICAL CONCENTRATIONS OF 5-ANDROSTENE-3BETA,17BETA-DIOL AND ITS METABOLISM IN MCF7 HUMAN BREAST CANCER CELLS.

Adams J, Garcia M, Rochefort H
Unite d'Endocrinologie Cellulaire Moleculaire, U 148 INSERM, 60, Rue de Navacelles, 34100 Montpellier, France
Cancer Res; 41(11,part1):4720-4726 1981

The compound 5-androstene-3beta,17beta-diol (ADIOL) has previously been shown to have a high affinity for the estrogen receptor and to translocate it to the nucleus in vitro and in vivo. This compound and related C19 delta5-steroids of adrenal origin have now been examined for their ability to in duce the synthesis in MCF7 cells of an estrogen-dependent secreted glycoprotein (mol wt 46,000). Concentrations required for half-max induction were 2 nM for ADIOL and 500 nM for dehydroepiandrosterone (DHEA). Dehydroepiandrosterone sulfate showed weak inducing ability at concentrations of 1 uM or greater. The induction by ADIOL was unaffected by the presence of an aromatase inhibitor, and 5alpha-androstane-3beta,17beta-diol, which cannot be aromatized, also induced the mol wt 46,000 protein at low concentrations. When cells were exposed to 10 nM [3H]ADIOL, the cytosol and nuclear fractions contained [3H]ADIOL resistant to charcoal adsorption. The bound [3H]ADIOL in the cytosol and nucleus was displaceable by 17beta-estradiol and tamoxifen, suggesting that it was binding to the estrogen receptor. [3H]ADIOL was metabolized to its 3beta-sulfate, which was excreted into the medium, and to [3H]DHEA, which was found in the cells and the medium as free DHEA and its 3beta-sulfate. [3H]DHEA was also metabolized by the cells to its 3beta-sulfate, to free ADIOL, and to the 3beta-sulfate of ADIOL. We conclude that: (a) ADIOL is effective as an estrogen in MCF7 cells at a concentration of 2 nM, which is within the range found in the blood of normal women; and (b) sulfurylation is a major route of inactivation of 3beta-hydroxy delta5-steroids in MCF7 cells. (Author abstract) (31 Refs)

2. ON THE OCCURRENCE AND TRANSPORT OF ESTRIOL-3-SULFATE IN HUMAN BREAST CYST FLUID: THE METABOLIC DISPOSITION OF BLOOD ESTRIOL-3-SULFATE IN NORMAL WOMEN.

Raju U, Noumoff J, Levitz M, Bradlow HL, Breed CN
(c/o Levitz) Dept. Obstetrics-Gynecology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016
J Clin Endocrinol Metab; 53(4):847-851 1981

The high concentration of estriol-3-sulfate (E3-3S) in human breast cyst fluid has been confirmed in 14 women with multiple cysts. The concentrations of E3-3S found in individual cysts drained within a short time span from the same patient were variable, the ratios ranging from unity to 40. After the iv administration of [14C]estriol or [3H]E3-3S, only minor accumulation of either isotope was detected in the cyst fluids aspirated 6.5-30 hr later. Since surprisingly small amounts of isotopes were found in blood, the metabolism of [3H]E3-3S was studied in two normal women. The test compound was injected iv, and blood samples were taken at intervals up to 7.5 hr. In addition, total urine was collected for 3 days. The blood clearance of [3H]E3-3S was rapid, with the half-life ranging from 15-30 min. However, E3-3S was only a minor component of the urine indicating rapid tissue extraction and metabolism rather than renal excretion for the compound. The studies indicate that E3-3S of human breast cyst fluid does not equilibrate rapidly with other body pools and that its uptake, if any, from the blood would be against a gradient. (Author abs tract) (22 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

3. EFFECT OF TOTAL PARENTERAL NUTRITION ON CORTISOL SECRETION DURING THE POSTOPERATIVE PERIOD.

Khmelevskii IaM, Sloventantor VIu, Shakhtarin VV, Seniukov MV, Kaplan MA, Zubov OG
Res. Inst. Medical Radiology, Obninsk, USSR
Vestn Akad Med Nauk SSSR; (8):73-77 1981

The effect of total parenteral nutrition (TPN) on the intra- and postoperative cortisol levels in the blood plasma was studied in 42 patients (40 men, 2 women; 32-67 yr old) with cancer of the larynx. The patients were divided into three groups: Group I (12 patients with metastases to the cervical lymph nodes) received postoperative nutrition through the probe, Group II (18 patients with primary cancer of the larynx) received combined treatment (preoperative radiotherapy at 4,000-6,000 rads and surgery) followed by TNP during the first 6 days of the postoperative period, and Group III (12 patients with primary cancer of the larynx) received combined treatment and TNP containing free amino acids. The patients in Groups II and III showed earlier normalization of cortisol levels. (12 Refs) (In RUS)

4. SERUM ANDROGEN LEVELS AND THE MENSTRUAL CYCLE IN WOMEN WITH BENIGN OR MALIGNANT BREAST DISEASE.

England PC, Sellwood RA, Knyba RE, Irvine JD
(c/o Knyba) Dept. Clinical Endocrinology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Clin Oncol; 7(3):213-219 1981

Serum levels of dehydroepiandrosterone sulfate have been determined in blood specimens taken over the menstrual cycle in 10 normal women and 28 patients with benign and malignant breast disease. There was no consistent or statistically significant correlation between the amounts of serum dehydroepiandrosterone sulfate and estradiol. This finding does not support the suggestion that the subnormal levels of androgens, in women with high risk of breast cancer and patients with a poor prognosis, reflect alterations in estrogen secretion. (Author abstract) (19 Refs)

5. PLASMA CONCENTRATIONS OF C-19 STEROIDS, ESTROGENS, FSH, LH AND PROLACTIN IN POST-MENOPAUSAL WOMEN WITH AND WITHOUT BREAST CANCER.

Bird CE, Cook S, Owen S, Sterns EE, Clark AF
Dept. Medicine, Etherington Hall, Queen's Univ., Stuart St., Kingston, Ontario K7L 2V7, Canada
Oncology; 38(6):365-368 1981

The plasma levels of 5alpha-dihydrotestosterone, testosterone, delta5-androstene-3beta,17beta-diol, delta4-androstenedione, dehydroepiandrosterone, estrone, estradiol, dehydroepiandrosterone sulfate, follicle stimulating hormone, luteinizing hormone and prolactin were measured in normal post-menopausal women and in post-menopausal women with proven breast cancer. The mean prolactin level was significantly higher (p less than 0.01) and the mean 5alpha-dihydrotestosterone level lower (p less than 0.05) for the women with breast cancer. There were no significant differences for any of the other hormones. As well, there were no significant differences for the extent of binding of testosterone and delta5-androstene-3beta,17beta-diol to plasma proteins between the two groups of subjects. (Author abstract) (29 Refs)

6. EFFECT OF METOCLOPRAMIDE ON PLASMA ALDOSTERONE IN NORMAL SUBJECTS, PRIMARY ALDOSTERONISM AND HYPOPITUITARISM.

Mantero F, Opocher G, Boscaro M, Valpione E, Armanini D, Fallo F
Istituto di Semeiotica Medica, via Ospedale Civile 105, 35100 Padova, Italy
Horm Metab Res; 13(8):464-467 1981

The behavior of plasma renin, aldosterone, cortisol and prolactin after administration of a drug with antidopaminergic action, metoclopramide, was evaluated in six normal subjects, eight patients affected by primary aldosteronism and in five patients affected by anterior hypopituitarism. In the first two groups, besides the predictable increase of prolactin under metoclopramide, a significant aldosterone increase was noted. Cortisol remained unchanged, and PRA was not significantly increased. A similar pattern of aldosterone, cortisol and PRA was also found in patients with hypopituitarism. However, the plasma prolactin did not increase in this group. The comparative examination of three groups of patients leads us to conclude that aldosterone increase is not imputable to ACTH, renin or to prolactin. This may be explained by a possible direct effect of the antidopaminergic drug at the adrenal level, which is more likely than an effect through some yet undetermined factor. (Author abstract) (14 Refs)

7. THYROTROPIC ACTIVITY OF THE PITUITARY GLAND AND BLOOD LEVELS OF TRIIODOTHYRONINE AND THYROXINE IN THE PATIENTS WITH UTERINE MYOMA.

Trubnikova LI
Dept. Obstetrics and Gynecology, Tadzhik Medical Inst., Dushanbe, USSR
Akush Ginekol (Mosk); (7):12-15 1981

Functional activity of the pituitary and thyroid glands was evaluated in 27 women (aged 22 to 42 yr) with uterine myomas. Determination of the blood levels of thyrotropin (TTH), thyroxine (T4), and triiodothyronine (T3) showed significant increase of TTH and estradiol with simultaneous decrease of T3 and T4 levels in the patients with ovulatory menstrual cycle. It was suggested that relationship between TTH, T3 and T4 in majority of the patients with uterine myoma reflected a primary insufficiency of the thyroid. (8 Refs) (In RUS)

8. DISSOCIATION OF CHORIOADENOMA DESTRUENS FROM HYDATIDIFORM MOLE BY URINARY STEROID ANALYSIS.

Kodama M, Kodama T, Totani K
Aichi Cancer Center, Res. Inst., Nagoya, Japan
Am J Obstet Gynecol; 141(3):288-293 1981

Dissociation between hydatidiform mole (HM) and chorioadenoma destruens (CA) was attempted by gas chromatographic analysis of urinary steroids. In the chromatogram, Fraction 2 (F 2) including four pregnane steroids (17-hydroxypregnenolone, pregnenolone, pregnanediol, and pregnanetriol) reflected the biologic activity of molar human chorionic gonadotropin (hCG), and the ratio of F2 to Fraction 1 (F1) (17-ketosteroids) was found useful in monitoring secondary growth of trophoblastic tumor: Urinary log F2/F1 after curettage declined quickly and unidirectionally in HM, but the same parameter exhibited a temporal rise in CA at 11 to 20 days after curettage because of the molar hCG from residual tumor tissue. The resolution between HM and CA at that stage (11 to 20 curettage days) was of the order of diagnostic use and superior to that with immunoreactive hCG. The data obtained are discussed in the light of pathophysiology of CA. (Author abstract) (15 Refs)

9. MEASUREMENT OF DIETHYLSTILBESTROL IN PLASMA FROM PATIENTS WITH CANCER OF THE PROSTATE.

Kemp HA, Read GF, Riad-Fahmy D, Pike AW, Gaskell SJ, Queen K, Harper ME, Griffiths K

(c/o Read) Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Heath, Cardiff, CF4 4XX, Wales

Cancer Res; 41(11,part1):4693-4697 1981

A specific radioimmunoassay has been developed for diethylstilbestrol (DES), using an antiserum raised against DES monocarboxymethyl ether and a tritium-labeled radio-ligand. Prior to radioimmunoassay, a fraction enriched in DES is obtained from a dichloroethane extract of plasma using Sephadex LH-20. The specificity of the assay is good, and the sensitivity (130 pg/ml) is adequate for accurate determination of DES in plasma from prostatic cancer patients treated with the drug. The precision is satisfactory, with an interassay coefficient of variation of approx 10% at concentrations of approx 1 ng/ml, and the blank values are negligible. Excellent agreement ($r = 0.96$) is observed between data obtained by radioimmunoassay and those obtained by a procedure using gas chromatography-high-resolution mass spectrometry. DES concentrations in the plasma of six treated (1 mg DES tds) patients were in the range 0.15 to 6.0 ng/ml. Increases in plasma concentration were observed within 2 hr of administration, with secondary rises occurring 5 to 6 hr later. Plasma testosterone concentrations were low in four of the patients; in a single subject, relatively high levels of testosterone were further elevated following administration of luteinizing hormone-releasing hormone. (Author abstract) (19 Refs)

10. HORMONAL ASPECTS OF PARENTERAL NUTRITION DURING INTENSIVE THERAPY OF CANCER PATIENTS.

Sudzhian AV, Rozanova NB

All-Union Cancer Res. Center, Moscow, USSR

Vestn Akad Med Nauk SSSR; (8):77-79 1981

The effect of parenteral nutrition (PN) on the hormonal status was studied in 83 patients with cancer of the stomach. Pre- and postoperative PN decreased cortisol, glucagon, and growth hormone levels, and increased insulin level. (10 Refs) (In RUS)

11. STRESS AND NEUROENDOCRINE SYSTEM IN CANCER PATIENTS.

Rylov VV, Sviridova SP, Guliaev GV
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (8):80-83 1981

The effect of surgery and anesthesia on the pituitary-adrenal system was studied in 54 patients with cancer of the stomach, 40 with lung cancer and 105 with breast cancer. The intraoperative changes in the level of corticotropin, somatotropin, and cortisol, as well as in the degree of glycemia depended upon the type of anesthesia. The increase in the levels of corticotropin and cortisol was correlated with the severity of postoperative complications. (3 Refs) (In RUS)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

12. CT FINDINGS AND GLUCOCORTICOID RECEPTORS IN INTRACRANIAL LESIONS WITH EDEMA.

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J Comput Assist Tomogr; 5(5):619-624 1981

Glucocorticoid receptors were measured in the surgical specimens of 19 intracranial tumors and 1 brain contusion. None of the patients had received any steroid treatment prior to the operation. Preoperative computed tomography (CT) scans of these patients were evaluated with respect to attenuation values, contrast enhancement, vol of the tumor and edema, and the other characteristics. These various findings were plotted against the amount of glucocorticoid receptors. There was some correlation between the amount of receptor and attenuation as well as contrast enhancement of the tumor. No definite correlation between the vol of edema and/or size of the tumor and the amount of receptor was found in the material taken in its entirety. However, in two tumor groups, namely meningiomas with marked edema and circumscribed, discrete gliomas, a tendency toward a high amount of glucocorticoid receptors was observed. The positive correlation with contrast enhancement, reinforced by reports in the literature that contrast enhancement is affected by steroids, corroborates the theory that the steroid-receptor interaction plays an important role in the vascular permeability of tumors. (Author abstract) (19 Refs)

13. GLUCOCORTICOID RECEPTORS AND IN VITRO RESPONSES TO GLUCOCORTICOID IN ACUTE NONLYMPHOCYTIC LEUKEMIA.

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Cancer Res; 41(11,part2):4853-4856 1981

Early clinical studies in which glucocorticoids were used alone in the treatment of acute nonlymphocytic leukemia (ANLL) reported a wide range of responses from remission in some patients to dramatic aggravation of the disease in others. In the hopes of identifying those patients likely to derive therapeutic benefit from glucocorticoids, we have studied glucocorticoid receptors and in vitro responses to glucocorticoids in 36 previously untreated adults with ANLL. The leukemic blasts of all patients contained glucocorticoid receptors (range, 4,300 to 28,400 total receptor sites per cell; median, 8,800). These receptors were similar in all respects studied to those from a variety of other normal and malignant tissues. There was little difference between receptor levels among the various French-American-British categories. In vitro responses to glucocorticoid were observed in leukemic blasts of 26 of 28 cases studied. These responses varied from near complete cell killing to stimulation of proliferation. Since the cells of patients with ANLL have about the same number of receptors as do cells from patients with acute lymphoblastic leukemia and these receptors are capable of mediating physiological responses in vitro, it is unlikely that qualitative or quantitative receptor defects underlie the relative resistance to glucocorticoid therapy of ANLL compared to acute lymphoblastic leukemia. However, the broad range of in vitro responses and receptor levels suggests that these studies might be useful in identifying those patients with ANLL likely to derive benefit from steroid therapy. (Author abstract) (23 Refs)

14. GLUCOCORTICOID RECEPTORS IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA.

Bloomfield CD, Smith KA, Peterson BA, Munck A
Univ. Minnesota Hosp., Box 277, Mayo Building, Minneapolis, MN, 55455
Cancer Res; 41(11,part2):4857-4860 1981

Glucocorticoid receptors were studied in leukemic cells from 14 newly diagnosed adults with acute lymphoblastic leukemia. Receptors were found in all cases; total receptor levels ranged from 1,348 to 18,697 sites per cell (median, 7,553). To determine the utility of glucocorticoid receptor levels for predicting response to glucocorticoid therapy, lymphoblasts were studied for receptors on nine occasions, and the patients were then treated with dexamethasone as a single agent. Response to glucocorticoid therapy appeared to correlate with lymphoblast receptor level. Five of six patients with greater than 4,500 total receptor sites per cell responded; all three patients with less than 4,500 receptors failed to respond. Glucocorticoid receptor level did not correlate with response to combination chemotherapy, duration of remission, or survival. Glucocorticoid receptors were studied at the initial presentation and following relapse in five patients. In two patients, the receptor level did not change following therapy; both patients at diagnosis had leukemias resistant to glucocorticoids. Three patients at relapse developed leukemias with lower receptor levels; these patients had leukemias sensitive to glucocorticoids at diagnosis. Our data suggest that the glucocorticoid receptor levels of lymphoblasts may be useful in predicting response to glucocorticoid therapy in adult acute lymphoblastic leukemia. They also suggest that, following relapse, cases initially sensitive to glucocorticoid may develop resistance by selection of cells with fewer receptors. (Author abstract) (17 Refs)

15. GLUCOCORTICOID RECEPTORS IN LYMPHOID TUMORS.

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Cancer Res; 41(11,part2):4861-4862 1981

There is a range of levels of glucocorticoid receptor numbers seen in the various subclasses of acute lymphatic leukemia (ALL). This variability cannot be explained by the known correlation between active cell proliferation and an increase in the number of receptors, since the tumors with the highest growth fraction (ie, Burkitt's lymphoma and T-cell leukemia) tend to have lower av receptor numbers than do tumors with lower growth fractions such as common ALL. All clinical specimens from patients with lymphatic leukemia have some measurable level of glucocorticoid receptors; therefore, the resistance seen in vivo cannot be explained by the lack of receptors. However, there has been a positive correlation, in our hands, with receptor level and prognosis. On the basis of in vitro models, it is proposed that perhaps the high receptor cell lines (ie, common ALL of childhood) have relative stability of their genetic material making glucocorticoid-resistant mutations less likely to occur in patients with these cells than in low-receptor cell lines (ie, T-cell leukemia). This greater genetic variability in the low-receptor lines could account for the earlier emergence of clinical glucocorticoid resistance in these patients. (Author abstract) (15 Refs)

16. EXPERIMENTAL AND CLINICAL ASPECTS OF HORMONE THERAPY OF BREAST CANCER.

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Arch Geschwulstforsch; 51(7):623-629 1981

Recent studies on the hormone therapy of advanced breast cancer are reviewed. Patients with relatively slowly growing tumors especially in the premenopausal period, patients with soft-tissue and lung metastases, and patients beyond the first 5 yr of menopause respond favorably to endocrine therapy. However, the remission rate in unselected patients is only 20-40% after ovariectomy, adrenalectomy, hypophysectomy, or androgen, estrogen, antiestrogen, or gestagen treatment. The determination of steroid hormone receptors is at present the best method for selecting the patients for endocrine therapy. The analysis of 1,336 cases showed a remission rate of 56% for estrogen receptor (ER)-positive and only 5.6% for ER-negative patients. A cooperative study covering 358 cases revealed remission rates of 77% for ER-positive and progesterone receptor (PR)-positive patients, 27% for ER-positive but PR-negative patients, 46% for ER-negative but PR-positive patients, and 11% for ER- and PR-negative patients. (16 Refs) (In GER)

17. HORMONE RECEPTORS IN THE THERAPY OF BREAST CANCER.

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Arch Geschwulstforsch; 51(7):637-641 1981

Therapy plan determined for patients with metastatic breast cancer on the basis of the estrogen receptor (ER) status is presented. Patients with ER-positive (ER+) and progesterone-positive (PR+) tumors are subjected to endocrine therapy only. Patients with ER+ and PR+ tumors and with good prognosis (slowly growing tumors, favorable localization of metastases, and patients who have long been in menopause) also receive endocrine therapy; however, those with unfavorable prognosis are subjected to polychemotherapy and endocrine therapy, while patients with ER- and PR-negative tumors are subjected to polychemotherapy. Adjuvant therapy for ER+ patients consists of oophorectomy and tamoxifen treatment before menopause, and of tamoxifen treatment only during menopause. Seventy-six Stage II patients treated according to these principles were followed up for 20 mo. Thirty-seven ER+ patients received endocrine treatment, the other 39 ER-negative patients were subjected to chemotherapy. The preliminary results were at least not more unfavorable with endocrine treatment than with polychemotherapy. The incidence of recurrences was 2/37 for the endocrine treatment and 8/39 in the chemotherapy group. (8 Refs) (In GER)

18. ESTRADIOL RECEPTORS IN RELATION TO CLINICAL PARAMETERS OF BREAST CANCER PATIENTS.

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Arch Geschwulstforsch; 51(7):631-636 1981

Correlations between estradiol receptors (ER) and clinical parameters were studied in 379 women with breast cancer. The percentages of ER-positive (ER+) patients were 36% among the premenopausal patients, 53.2% within the first 5 yr, and 47.6% beyond the first 5 yr of menopause. The percentages of ER+ cases among 347 patients, were 39.1% in Stage I, 54.7% in Stage II, 40.1% in Stage III, and 22.9% in Stage IV. ER+ status correlated with axillary lymph node involvement in 346 patients was 48.8% without lymph node involvement, 50.7% with 1-7 affected lymph nodes, and 34.7% for more than 7 affected lymph nodes. The ER+ receptor status for the different histological types in 366 cases was 50% of all solid simple carcinomas, 33.3% of medullary carcinomas, 34.9% of scirrhous carcinomas, 57.9% of tubular carcinomas, 66.9% of cribriform carcinomas, and 25.9% of other histological types. The tumor-free period, evaluated for 93 cases, averaged 23.2 mo for 35 ER+ patients and 17.2 mo for 58 ER-negative (ER-) patients. Mean survival was 40.11 mo for the ER+ and 22.23 mo for the ER- patients. The receptor status in primary tumor and lymph node metastases was compared in 195 cases: both were ER+ in 90 cases (46.15%) and ER- in 67 cases (34.36%). The primary tumor was ER+ and the lymph node metastasis negative in 14 cases (7.18%), and vice versa in 24 cases (12.31%). The findings indicate with some exceptions, the percentage of ER+ tumors is higher in cases with favorable prognosis. (14 Refs) (In GER)

19. A TWO-STAGE IMMUNOCYTOCHEMICAL METHOD FOR OESTROGEN RECEPTOR ANALYSIS: CORRELATION WITH MORPHOLOGICAL PARAMETERS OF BREAST CARCINOMAS.

Eusebi V, Cerasoli PT, Guidelli-Guidi S, Grilli S, Bussolati G, Azzopardi JG
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Tumori; 67(4):315-323 1981

An immunocytochemical method for estrogen receptor (ER) analysis of breast carcinomas is described and compared with the dextran-coated charcoal (DCC) assay and a cytochemical method. The method described is superior to the purely cytochemical, especially in terms of sensitivity, demonstration of nuclear receptors and correlation with the DCC assay. The DCC assay is reliable except in the case of poorly cellular tumors: in these the immunocytochemical method is far superior, being independent of tumor cellularity. With this new method, lobular carcinomas are shown to the ER-rich compared with their ductal counterparts, a conclusion currently disputed, largely because methods employed mostly fail to take account of tumor cellularity. A combination of the DCC assay and the immunocytochemical method here described gives the max information about the ER-status of a particular carcinoma. (Author abstract) (25 Refs)

20. ABSENCE OF SEASONAL VARIATION OF ESTROGEN RECEPTOR LEVELS IN HUMAN BREAST CANCER TISSUE.

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Mol Cell Endocrinol; 23(3):265-273 1981

Between 1975 and 1978, 979 human primary breast cancer tumors (HPBCT) were collected, frozen, within 2 wk cytosol without lipids prepared, and estradiol receptors quantitatively determined by the modified European Organization for Research on the Treatment of Cancer procedure. Of 979 HPBCT, 631 classified receptor positive were derived from 212 premenopausal and 419 postmenopausal patients. Results for the two groups were statistically analyzed separately and combined; analyses do not support the existence of any periodicity in estrogen receptor level with seasonal variation consistent from yr to yr. (16 Refs)

21. FAILURE OF ESTRADIOL IMMUNOFLUORESCENCE IN MCF-7 BREAST CANCER CELLS TO DETECT ESTROGEN RECEPTORS.

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Cancer Res; 41(11,part1):4644-4652 1981

An indirect immunofluorescence assay was used to detect estradiol in MCF-7 breast cancer cells to determine if the estradiol-specific fluorescence observed represented estrogen receptor-bound estradiol. Appropriate controls were used to demonstrate the immunological specificity of our assay procedures. Initial studies of estradiol binding in MCF-7 cells were performed at 20 C for 1 hr with different concentrations of estradiol. Cytoplasmic and nuclear staining were observed following treatment with 10 nM estradiol, but not with lower concentrations which were nevertheless still sufficient to saturate the estrogen receptor. The staining intensity increased with higher estradiol concentration, which is consistent with estradiol binding to lower-affinity binding sites. In order to further determine if estradiol binding by the estrogen receptor was being detected, we pretreated MCF-7 cells with 5 nM diethylstilbestrol at 37 C for 1 hr to translocate all the estrogen receptor to the nucleus and then administered estradiol at varying concentrations for 4 hr at 4 C. The estradiol was still primarily detected in the cytoplasm, although virtually all of the estrogen receptor was found to be present in the nucleus by standard [3H]estradiol binding assays. Additional immunochemical studies using sucrose gradient analysis to detect antibody-estradiol-receptor complexes clearly established that these complexes could not be detected. The present results suggest that, although immunocytochemical assays can specifically detect estradiol in MCF-7 cells, the estradiol is bound to lower-affinity binding sites rather than to the estrogen receptor. Saturation analyses of intact viable MCF-7 cells performed at 37 C for 30 min using [3H]estradiol at concentrations ranging from 0.1 to 93 nM revealed additional lower-affinity estradiol-binding sites besides the receptor, perhaps analogous to the Type II sites reported in the rat uterus and human breast cancers. (Author abstract) (45 Refs)

22. TAMOXIFEN AZIRIDINES: EFFECTIVE INACTIVATORS OF THE ESTROGEN RECEPTOR.

Robertson DW, Wei LL, Hayes JR, Carlson KE, Katzenellenbogen JA, Katzenellenbogen BS
Dept. Chemistry, Univ. Illinois., Urbana, IL, 61801
Endocrinology; 109(4):1298-1300 1981

Two analogs of the antiestrogen tamoxifen, which bear a chemically reactive aziridine function in place of the dimethylamino group, bind to the estrogen receptor from rat uterus and from MCF-7 human breast cancer cells and appear to react irreversibly with the receptor at the estrogen binding site, in a time-and concentration-dependent fashion. Because these compounds are effective receptor inactivators in uterus and breast cancer cells, they should prove to be useful probes for investigating the role of receptor in regulating cellular responses to estrogen and in studying the dynamics of estrogen receptor synthesis and turnover. (Author abstract) (9 Refs)

23. ESTROGEN AND PROGESTERONE BINDING PROTEINS IN HUMAN COLORECTAL CANCER. A PRELIMINARY CHARACTERIZATION OF ESTRADIOL RECEPTOR.

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Tumori; 67(4):307-314 1981

Estradiol receptor (ER) and progesterone receptor (PgR) were assayed in tumors from 20 patients with primary colorectal cancer. Ten of 20 tumors contained high affinity sites for 17beta-estradiol and progesterone. The highest concentration of ER was 56 fmol/mg of protein. The ER dissociation constant ranged from 1.6 x 10(-10) M to 8 x 10(-10) M (mean 4.6 +-2.6). The highest concentration of PgR was 42 fmol/mg of protein. The PgR dissociation constant ranged from 3 x 10(-9) to 9 x 10(-9) M (mean 5.65 +-2.1). Four out of 20 specimens analyzed were from male patients and all resulted negative for both receptors. Sixty percent of ER positive tumors were also PgR positive, whereas only 20% of ER negative were PgR positive. Sucrose gradient centrifugation showed that cytoplasmic ER of colorectal cancer sedimented at 3 S in the absence of protease inhibitors and at 4.5 S in the presence of 1 mM phenylmethylsulphonyl fluoride (PMSF) both in low and in high ionic strength. When chromatographed on Sephadex G-200 almost all ER was quantitatively recovered in the included fractions. Mol wt of ER eluted from Sephadex G-200 ranged from 90,000 to 50,000 daltons. Elution profile and mol wt heterogeneity suggest that, in spite of the presence of PMSF, there is a limited proteolysis of ER. Partially purified colorectal cancer ER did not bind to sepharose-heparin. The isoelectric point of ER was 6.4-6.5. (Author abstract) (35 Refs)

24. INDUCTION OF GLUCOCORTICOID-RESISTANT VARIANTS IN A MURINE THYMOMA LINE BY ANTITUMOR DRUGS.

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Cancer Res; 41(11,part1):4540-4546 1981

Several antitumor drugs are shown to be mutagenic in murine thymoma lines: mitomycin C, bleomycin, streptonigrin, Colcemid, and BD40, an analog of ellipticine. Using conditions yielding 3 to 40% cell survival, all five drugs tested increase the frequency of glucocorticoid-resistant variants. Mitomycin C is as efficient as the classical alkylating agents N-methyl-N'-

nitro-N-nitrosoguanidine and ethyl methanesulfonate. The other drugs, previously untested for mutagenic activity on mammalian cells, are weak mutagens yielding variants at frequencies one to two orders of magnitude lower t han the alkylating agents. All 152 variants obtained result from defects in the glucocorticoid receptor. Variants induced by mitomycin C, streptonigrin, Colcemid, and BD40 have very reduced receptor activity, as measured by dexamethasone binding. In contrast, bleomycin or the combination of mitomycin C and dexamethasone induce a majority of variants having dexamethasone-binding activity comparable to the parental line. However, assays of nuclear transfer capacity and genetic complementation show that these receptors are nonfunctional and may result from point mutations in the gene encoding the glucocorticoid receptor. This study suggests that, in combination therapies, antitumor drugs might induce glucocorticoid-resistant lymphoid cell variants that could be selected by the hormone. (Author abstract) (27 Refs)

25. ESTROGEN RECEPTOR-LIKE MACROMOLECULE IN MTTW15 RAT PITUITARY TUMORS: EFFECTS OF ANTIESTROGENS.

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Mol Cell Endocrinol; 23(3):333-344 1981

Antiestrogen studies were performed to gain further insight into estrogen action in MtTW15 rat pituitary tumors. Highly inbred young adult male and female Wistar/Furth rats were inoculated with MtTW15 mammosomatotropic tumor fragments. The 2,4,6,7-[3H](N)-estradiol-17beta (E2) and synthetic progestin [medroxyprogesterone acetate (MPA)] treatments started 1 wk after inoculation, and lasted 7 wk; 1 wk later animals were killed by decapitation. Specific cytosol E2 binding (approx 3 picomoles/g tumor) was detected in all animals. In general, tumor cytosol from male rats bound more E2 than that of their female counterparts. Sucrose density gradient sedimentation resulted in a peak at approx 7S for E2-binding macromolecule; these E2 binding sites were specific for estrogenic steroid. There were no differences in steroid binding specificity for tumors derived either from male or female hosts. Increasing the temperature from 4 to 18 C shifted the sedimentation coefficient from 7 to 3.5S. Trypsin promoted degradation of E2-binding macromolecule, but not DNAase or RNAase. Antiestrogens nafoxidine, tamoxifen, trioxifene, and LY117018 reduced cytosolic estrogen receptor levels, promoted tumor growth, significantly inhibited the concentration of unoccupied E2-binding sites in tumor cytosol, and competed for E2 binding sites in vitro; they stimulated production of growth hormone while having no meaningful effect on production of prolactin. MtTW15 tumor may provide a useful model for the study of antiestrogen agonist and antagonist properties. (22 Refs)

26. THE EFFECTS OF IONIZING RADIATION AND OESTROGEN TREATMENT ON THE STEROID-RECEPTOR CONCENTRATIONS IN EXPERIMENTAL MAMMARY CARCINOMA.

Janssens JP, Wittevrongel C, Van Dam J, Goddeeris P, Lauwerijns JM, De Loecker M
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Biochem Soc Trans; 9(1):95-96 1981

Mammary carcinoma was induced in Sprague-Dawley rats by intragastric injection of 7,12-dimethylbenz[a]anthracene. Tumors appeared after 3 mo. Some rats were irradiated with 20 Gray from a cobalt teletherapy source. Some were treated for three days by sc injection of 5 ug 17beta-estradiol (EDB). Controls remained untreated. Steroid receptor concentrations were determined 40 hr after final hormone treatment or up to 65 days after irradiation. Tumor regression to 25% of pretreatment size occurred during the first 30 days after irradiation. Renewed growth followed, reaching 90% of the pretreatment size by 65 days. EDB-receptor concentrations fell from 2.56 femtomoles/mg (fm/mg) to 1.09 fm/mg during the first 30 days. They remained at the low level during tumor regrowth. Progesterone-receptor levels fell from a control level of 7.39 fm/mg to 1.83 fm/mg during tumor regression and increased during tumor regrowth to 2.36 fm/mg at 65 days. EDB treatment at 65 days restored progesterone-receptor levels to normal control values. EDB-receptor concentrations were not affected by EDB treatment. Evidently the EDB-receptor system, which is necessary for the stimulation of the progesterone-receptor system, remains intact and active after irradiation, although the concentration of receptors is reduced. Interpretation of receptor concentrations measured during endocrine and radiation therapy should be made as a function of these factors. (9 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

27. THE RELATIVE EFFECTIVENESS OF RADIATION THERAPY, CORTICOSTEROIDS, AND SURGERY IN THE MANAGEMENT OF MELANOMA METASTATIC TO THE CNS SYSTEM.

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Int J Radiat Oncol Biol Phys; 7(7):897-906 1981

Various treatment modalities were studied retrospectively in patients with melanoma metastatic to the CNS. Among the 63 patients, 25 had multiple brain metastases (MBM) and 38 solitary brain metastases (SBM). The 41 males and 22 females ranged in age from 18-78 yr. Various antineoplastic agents were employed. Corticosteroids were given to 49 patients 2-7 days before radiation therapy (RT); 73% showed documented response to the agents, which was substantially higher than the 42% response rate to RT. RT led to response in 52% with SBM and 30% with MBM. Large doses (500 rad or greater per fraction) produced significantly greater response than smaller doses, although fraction size had no effect on duration of response or survival. Surgical excision of SBM with RT had significantly longer av response (405 days vs 57 days) and survival (448 days vs 96 days) than did SBM who did not receive surgery. Second RT courses relieved recurrent neurological symptoms, but responses were short and without influence on survival. Four of seven patients with cord compression who underwent decompressive laminectomy showed neurological improvement; postoperative RT led to no further improvement. Two patients with cord compression who were paraplegic did not response to RT. Surgical excision with postoperative RT is recommended for management of SBM from melanoma. (34 Refs)

28. NEW ASPECTS IN THE DEVELOPMENT OF CYTOTOXIC-LINKED ESTROGENS FOR THE CONTROL OF BREAST NEOPLASIA.

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Arch Geschwulstforsch; 51(7):643-649 1981

The selection and use of cytotoxic-linked estrogens, which bind to estrogen receptors (ERs) and thereby specifically concentrate in the target tissues including breast neoplasms, are described. The selection of these agents is based upon their binding ability to cytoplasmic ERs, their cytotoxicity against two human breast cancer cell lines (ER+ MCF-7 and ER- Evas-T), and their endocrinologic properties and toxicology. Four epoxide derivatives of 17-beta-estradiol and 17-alpha-estradiol were found to reversibly bind with ER but showed no cytotoxicity against MCF-7 and Evsa-7 cell lines. Nitrogen mustard derivatives of hexestrol, diethylstilbestrol, and estrone displayed binding affinity for ER and cytotoxicity against MCF-7 cells. Only the two mononitrogen mustard derivatives of estrone inhibited growth of Evsa-7 cells. This indicated that these nitrogen mustard derivatives had a weaker effect on the Evsa cell line, consistent with the hypothesis of a participation of ERs in their cytotoxic action. The results indicated that the linking of a cytotoxic group on an estrogen in an appropriate position can yield a drug with a significant binding affinity for ERs. The therapeutic implications of these findings are discussed. (13 Refs)

29. DIFFERENT EFFECTS OF OESTRADIOL, OESTRIOL, OESTETROL AND OF OESTRONE ON HUMAN BREAST CANCER CELLS (MCF-7) IN LONG TERM TISSUE CULTURE.

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Acta Endocrinol (Copenh); 98(1):73-80 1981

The effects of estradiol (Oe2), estrone (Oe1), estriol (Oe3), estetrol (Oe4) on the induction of the progesterone receptor (PgR) and growth of MCF-7 cells are compared. All the four estrogens increase cell PgR concentration. Analysis of the dose-response curves shows induction by Oe2 to be 10x and 50x greater than Oe3 and Oe4, respectively. Oe1 and Oe2 are equally effective, even with consideration of metabolic conversion of Oe1 into Oe2. When compared with untreated cells, Oe2, Oe3 and Oe4 do not influence significantly the plating efficiency but all three hormones increase thymidine incorporation of cells in log phase growth. Oe2, Oe3 and Oe4 are able to rescue the growth inhibition induced by antiestrogens. The respective potency compared to Oe2 is again in the range of 10 and 50x lower for Oe3 and Oe4, respectively. On the other hand Oe1 decreases plating efficiency, thymidine incorporation and does not rescue the growth inhibition induced by antiestrogens when the metabolic conversion of Oe1 into Oe2 is prevented. Thus, Oe3 and Oe4 behave like complete Oe2 agonists whereas Oe1 has dissociated effects, agonist on PgR induction and antagonist on cell growth. (Author abstract) (24 Refs)

30. AN ANTIESTROGENIC ACTION OF ANDROGENS IN HUMAN BREAST CANCER CELLS.

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J Clin Endocrinol Metab; 53(4):836-842 1981

We have recently observed that androgens prevent the estrogen-dependent augmentation of cytoplasmic progesterone receptor (PRc) in MCF-7 human breast cancer cells and now report the results of studies that further characterize this new example of sex steroid antagonism. Using a single saturating dose assay to monitor changes in MCF-7 PRc concentration, we have observed that androgens are capable of inhibiting both the estrogenic induction and the ongoing stimulation of PRc synthesis, but have no apparent effect upon basal concentrations of this receptor. Both testosterone and dihydrotestosterone (DHT) demonstrate similar degrees of antiestrogenic activity at concentrations between 10(-10)-10(-8) M. Furthermore, a 10(-8)-M concentration of either androgen completely inhibits the stimulation of PRc synthesis by 10(-11)-10(-8) M 17beta-estradiol (E2). This inhibitory effect is maintained during the continued presence of either testosterone or DHT, but rapidly disappears after the withdrawal of androgen from the culture medium. The specific nuclear binding of 17beta-[3H]estradiol over time appears to be similar in cultures incubated in the presence and absence of 10(-8) M DHT. This observation suggests that androgens do not inhibit estrogen action by interfering with the formation, activation, nuclear binding, or nuclear processing of estrogen-receptor complexes. The estrogenic stimulation of PRc is not diminished by the 5beta-epimer of DHT, and the inhibitory activity of DHT itself is blocked by several different antiandrogens. These findings provide substantial support for the concept that the antiestrogenic effect of androgens is mediated by an androgen receptor mechanism. These results may provide new insights into the clinically apparent antagonistic effects of estrogens and androgens upon both normal and malignant human breast tissues. (Author abstract) (21 Refs)

31. EFFECTS OF HIGH-DOSE METHOTREXATE AND VINCRISTINE ON OVARIAN AND TESTICULAR FUNCTIONS IN PATIENTS UNDERGOING POSTOPERATIVE ADJUVANT TREATMENT OF OSTEOSARCOMA.

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Cancer Treat Rep; 65(9):739-746 1981

We have studied gonadal function in five patients (3 men and 2 women) who received high-dose methotrexate (HD-MTX) alone and in 12 patients (7 men and 5 women) who received HD-MTX and vincristine (VCR) as postoperative adjuvant therapy for osteosarcoma. Testicular function was assessed by determination of testicular size, sperm concentration, and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels while evaluation of ovarian function was based on menstrual history and serum FSH, LH, estradiol, and progesterone levels. The two women who received HD-MTX and all five women who received HD-MTX and VCR had regular cyclic menses not only after therapy but also during treatment. Serum FSH, LH, estradiol, and progesterone levels were normal in all women studied. Among the 10 men studied, testicular function was normal in the 6 patients evaluated initially several mo after the completion of therapy. In contrast, severe oligospermia was noted among four men evaluated during and immediately after treatment. From serum samples obtained before, during, and after treatment we have determined that approx one half of the men who received HD-MTX alone or in combination with VCR develop transient testicular failure associated with a significant increase in serum FSH but not LH levels. Sperm concentration and serum FSH levels then return to normal after completion of chemotherapy. (Author abstract) (46 Refs)

32. LIPID PATTERNS IN VAGINAL CELLS EXFOLIATED FROM DIFFERENT PHYSIOLOGIC CONDITIONS.

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Dept. Endocrinology, Chittaranjan Natl. Cancer Res. Centre, 37 S.P. Mukherjee Road, Calcutta 700 026, India
Acta Cytol (Baltimore); 25(5):572-577 1981

A comprehensive study was made of the patterns of lipid granules in vaginal cells exfoliated during different hormonal states as well as under neoplastic conditions. The influence of in vitro incubation with estrogen and progesterone on the lipid patterns in cells exfoliated from normal and cancerous cervices was also investigated. The results clearly indicated the influence of sex hormones on the size and distribution of the lipid granules. While estrogen increased the fine lipid granules, as evident during the estrogenic phase of the menstrual cycle, progesterone influenced the coarse granules, which increased during the progestational phase and pregnancy. Similar responses were observed in the in vitro studies. The significance of the fine and coarse granules in different conditions is discussed in light of both the alteration of the metabolic process governing the synthesis of these components and the conversion of fine granules to coarse granules under such conditions. (Author abstract) (16 Refs)

33. EFFECTS OF HYDROCORTISONE ON THE SYNTHESIS OF EPSTEIN-BARR VIRUS ANTIGENS IN P3HR-1 CELLS.

Prachova K, Roubal J
Dept. Experimental Virology, Inst. Sera and Vaccines, 181 03 Prague, Czechoslovakia
Acta Virol (Praha); 25(3):163-166 1981

Hydrocortisone was capable of enhancing the synthesis of Epstein-Barr virus antigens in producer P3HR-1 cells which had been induced with a 24-hr pulse of 5-iodo-2-deoxyuridine. The effect of hydrocortisone was time dependent, suggesting that an early step in the induction process, and not the antigen synthesis itself, was influenced by the drug. (Author abstract) (10 Refs)

34. STEROIDS INHIBIT TUMOR PROMOTING AGENT INDUCED EPSTEIN-BARR VIRUS EARLY ANTIGENS IN RAJI CELLS.

Sundar SK, Ablashi DV, Armstrong GR, Zipkin M, Faggioni A, Levine PH
Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Int J Cancer; 28(4):503-507 1981

Four steroids and one protease inhibitor were evaluated for their effects on 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced and Epstein-Barr virus-induced early antigens (EBV-EA) in Raji cells. Continuous treatment with dexamethasone, prednisolone, hydrocortisone and cortisone inhibited TPA-induced EBV-EA to varying degrees, but the protease inhibitor N-alpha-p-tosyl L-lysine chloromethyl ketone-HCl (TLCK) had no significant effect. None of the agents tested inhibited EBV-induced EA. In addition, the effect of the steroids was reversible since the removal of these agents resulted in recovery of the percentage of EBV-EA-positive cells in TPA-treated cultures. These results were in agreement with the in vivo experiments of other investigators, who demonstrated inhibition of tumor promotion with steroids. Since TLCK failed to inhibit TPA-induced EA, it is unlikely that induction of EA by TPA is the result of production of proteases. (Author abstract) (36 Refs)

35. EFFECT OF BROMOCRIPTINE, SOMATOSTATIN, AND OESTRADIOL-17BETA ON HORMONE SECRETION AND ULTRASTRUCTURE OF HUMAN PITUITARY TUMOURS IN VITRO.

Prysor-Jones RA, Kennedy SJ, O'Sullivan JP, Jenkins JS
Dept. Medicine, St. George's Hosp. Medical Sch., London, SW17 ORE, England
Acta Endocrinol (Copenh); 98(1):14-23 1981

The effect of bromocriptine and somatostatin on hormone secretion and the ultrastructure of human pituitary adenomas was studied in vitro. Prolactin secretion was inhibited by bromocriptine in 3 out of 10 prolactin-secreting tumors and in explants from two normal pituitaries. GH secretion was reduced by bromocriptine in four out of six GH-secreting adenomas but was not affected by the drug in the incubations of normal pituitaries. Somatostatin inhibited GH secretion in two out of five pituitary adenomas and the effect was comparable with that of bromocriptine. Incubation of prolactin-secreting adenomas with estradiol for a long as 24 days produced no change in hormone secretion. Examination of tumor explants by electron microscopy showed that somatostatin and bromocriptine produced accumulation of secretion granules but no changes in the secretory organelles. Long term bromocriptine treatment of 'nude' athymic mice bearing xenografts of human pituitary adenomas suppressed hormone secretion and produced some increase in secretion granules but there were no morphological changes in the secretory organelles or other vital structures of the adenoma cells. (Author abstract) (27 Refs)

36. GLUCOCORTICOID-MEDIATED INHIBITION OF ORNITHINE DECARBOXYLYASE ACTIVITY IN S49 LYMPHOMA CELLS.

Insel PA, Honeysett JM
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Proc Natl Acad Sci USA; 78(9,part2):5669-5672 1981

Incubation of wild-type S49 lymphoma cells with glucocorticoids, such as dexamethasone and hydrocortisone, inhibits the activity of ornithine decarboxylase (L-ornithine carboxylyase, EC 4.1.1.17), the rate-limiting enzyme in the pathway of polyamine biosynthesis. The kinetics of this inhibition are more rapid than the glucocorticoid-mediated growth arrest in the G1 phase of the cell cycle or in glucocorticoid-mediated cytolysis of these cells. The inhibition of ornithine decarboxylase activity by corticosteroids is specific for steroids of the glucocorticoid class. Results obtained with variant S49 cells having lesions in the pathways of glucocorticoid or cyclic AMP action indicate that cytoplasmic glucocorticoid receptors, as well as nuclear transfer of steroid-receptor complexes, are required for the inhibition of ornithine decarboxylase activity but that this inhibition does not require hormonal activation of adenylate cyclase or cyclic AMP-dependent protein kinase. Because glucocorticoid-mediated inhibition of ornithine decarboxylase occurs when cellular protein synthesis has decreased less than 20%, this inhibition may represent a specific glucocorticoid-mediated deinduction of ornithine decarboxylase in S49 cells. Inhibition of ornithine decarboxylase activity may offer a useful marker for suppression of growth and cell cycle progression in these and other lymphoma cells. (Author abstract) (33 Refs)

37. DEXAMETHASONE EFFECT ON THE GROWTH RATE, THE PLASMINOGEN ACTIVATOR, AND THE MMTV DEPENDENT DNA POLYMERASE IN A MOUSE MAMMARY TUMOR CELL LINE.

Failly-Crepin C, Fromont S, Crepin M
Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94802 Villejuif Cedex, France
Biochem Biophys Res Commun; 102(1):22-29 1981

The effect of dexamethasone (DMS) was studied in cultured cells of murine mammary gland carcinoma (GR cells). DMS caused inhibition of exponential growth but not overall protein synthesis. Treatment with DMS resulted in significant inhibition of extra- and intracellular plasminogen activator. Reverse transcriptase associated with secreted murine mammary tumor virus particles was strongly stimulated. (20 Refs)

38. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

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Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed after 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extrahepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

39. RAT MAMMARY CARCINOMA CELLS SECRETE ACTIVE COLLAGENASE AND ACTIVATE LATENT ENZYME IN THE STROMA VIA PLASMINOGEN ACTIVATOR.

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Int J Cancer; 28(4):509-515 1981

A spontaneous mammary adenocarcinoma (AC) from an inbred female rat was investigated with regard to secretion of neutral proteases. Cultures of neoplastic epithelial cells derived from the tumor secreted an enzyme that fulfilled the criteria for a specific collagenase. In contrast to cultures of non-neoplastic cells, tumor collagenase was present as an active enzyme, since treatment with trypsin or p-aminophenylmercuric acetate (APMA) did not increase activity. The neoplastic cells were also prolific producers of plasminogen activator (PA). Dexamethasone (Dex)(10(-6) M) markedly reduced the levels of both enzymes. Addition of tranexamic acid (TA), an inhibitor of plasmin and of plasminogen activation, did not affect collagenase activity, even at 10(-1) M TA, nor did latent collagenase accumulate. Latent collagenase was secreted in culture by normal fibroblasts from neonatal rat lungs. This latent enzyme was activated by the addition of tumor cell medium plus plasminogen, but this effect was inhibited by the addition of TA. These results demonstrate that the neoplastic cells themselves secrete collagenase as an active enzyme. PA is also secreted, is not involved with tumor collagenase, but is capable, in the presence of plasminogen, of activating latent collagenase produced by the non-neoplastic cells within the tumor or in the surrounding tissue. This tumor possesses potent collagenolytic ability in vitro which may be partly responsible for its rapid invasion in vivo. (Author abstract) (36 Refs)

40. BIOSYNTHESIS AND HORMONE-REGULATED EXPRESSION OF SECRETORY GLYCOPROTEINS IN RAT LIVER AND HEPATOMA CELLS. EFFECT OF GLUCOCORTICOIDS AND INFLAMMATION.

Baumann H, Held WA
Dept. Cell and Tumor Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Biol Chem; 256(19):10145-10155 1981

Exposure of rat hepatoma tissue culture cells to dexamethasone results in appearance of a new glycoprotein, gp35-50 (Mr = 35,000 to 50,000) and increased synthesis of another glycoprotein, gp50 (Mr = 50,000). The glycoproteins synthesized in a fractionated cell-free translation system (containing dog pancreas microsomes) appear as a well separated series of spots on two-dimensional polyacrylamide gels which differ in size and charge. Glycoproteins synthesized by glucose-starved cells show similar size and charge heterogeneity. The size heterogeneity consists of a series of spots, each differing in mol wt by about 3,000, which could be almost completely abolished by treatment with endo-beta-N-acetylglucosaminidase H. Our results indicate that unglycosylated gp50 (Mr = 42,000) typically acquires three N-glycan units, whereas gp35-50 (Mr = 22,000) possesses eight N-glycosylation sites. Analysis of the cell-free translation products directed by mRNA from hepatoma tissue culture cells grown in tissue culture, from hepatoma tissue, and from normal liver tissue indicated that administration of dexamethasone causes a pronounced increase in gp35-50 mRNA in all three tissues. A similar increase was observed in liver after inflammation which along with other biochemical properties suggests that gp35-50 may be alpha1-acid protein. In contrast, mRNA coding for gp50 was not increased by dexamethasone in tumor tissue and no protein structurally related to gp50 was detected in the liver mRNA translation products. Thus, gp35-50 is expressed in normal liver, whereas gp50 is expressed in hepatoma cells and is differentially regulated by steroid hormones depending on whether the cells are grown in tissue culture or as a tumor in the rat. (Author abstract) (53 Refs)

41. LUTROPIN RECEPTORS IN NORMAL AND TUMOUR LEYDIG CELLS.

Cooke BA, Dix CJ, Magee-Brown R
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Biochem Soc Trans; 9(1):40-42 1981

Leydig cells from normal adult mouse and rat testes and a Leydig cell tumor can be separated into two cell populations (both containing lutropin receptors) which differ in density and steroidogenic responsiveness. The etiology of these cell types is unknown. They may reflect different phases in a cell cycle. Treatment with gonadotropin (lutropin or human choriogonadotropin) in vivo has been shown to result in the loss of lutropin receptors, a reduction in adenylate cyclase activity, and reduced steroidogenesis; treatment of rats with gonadotropin results in reduced sensitivity of Leydig cells to lutropin in vitro. Tumor cells of density 1.07 g/ml were exposed in vitro to lutropin (0.0, 10, 100, or 1,000 nanog/ml) and exhibited an initial increase in number of lutropin receptors. This reached a max in the controls after 2 hr and remained constant thereafter. All lutropin-treated cells showed decreased binding of choriogonadotropin after 1-2 hr incubation. Basal production of cyclic AMP initially reflected pretreatment with lutropin. Cyclic AMP rose sharply within 1 hr and returned to normal pretreatment levels by 4 hr. Reduction in binding of choriogonadotropin was inhibited by cycloheximide, which prevented lutropin-induced desensitization of adenylate cyclase activity. Results indicate that desensitization of Leydig cells can be induced in vitro, and loss of both lutropin receptors and adenylate cyclase activity occurs simultaneously; both processes depend on protein synthesis. (16 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

42. PREOPERATIVE IRRADIATION AND RADICAL EXTIRPATION OF MALIGNANT BRAIN TUMORS (MEETING ABSTRACT).

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Dept. Neurosurgery, Natl. Medical Center Hosp., Shinjuku-ku, Tokyo 162, Japan
Program and Abstracts of the 22nd Annual Meeting of Japanese Society of Neurology held in Kumamoto, Japan, 20-22 May, 1981. Japanese Society of Neurology, Tokyo 113, Japan, 282 pp., 1981.

Brain tumors were extirpated from 13 patients (11 neurogliomas including 1 brain stem tumor, 1 medulloblastoma and 1 embryonal carcinoma) who had preoperative irradiation (10 Gy/x, total dose 50-60 Gy) before which an accurate diagnosis had been made by computed tomography (CT) and other tests. Continuous cerebral ventrical drainage or ventriculo-peritoneal-shunt and steroids were used when the internal pressure of the cranium was high. Surgery was performed within 10 days after radiation therapy was completed. Various changes in the tumor were observed after radiation therapy by CT scanning: reduction in the diameter of the tumor, appearance of low-absorbing areas in the tumor, no change or a slight increase in tumor size. Most of the patients had edema, but it could be controlled well with steroids. Angiography showed regression of tumor blood vessels. There was little hemorrhage in most of the patients during surgery, and in some patients the borderline between the tumor and normal brain became clear. Generaly, the tumor could be extirpated en bloc. Histopathologically, necrosis and fibrosis were observed in some of the tumor tissues, but tissue that had not been affected at all was also observed. Total resection, subtotal resection and partial resection was performed on four, six and three patients, respectively, and complete control could be expected for the four patients who had total resection. Postoperative recovery was satisfactory with no incomplete suture of the skin, and except for two patients with brain stem tumors that had spread to both right and left hemispheres, the patients returned to normal life. (no Refs) (In JPN)

43. POTENTIAL ANTIESTROGENS. SYNTHESIS AND EVALUATION OF MAMMARY TUMOR INHIBITING ACTIVITY OF 1,2-DIALKYL-1,2-BIS(3'-HYDROXYPHENYL)ETHANES.

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J Med Chem; 24(10):1192-1197 1981

The synthesis of the meso-1,2-dialkyl-1,2-bis(3'-hydroxyphenyl)ethanes [alkyl substituent: CH3 (19), C2H5 (20), C3H7 (22), C4H9 (23), i-C4H9 (24), and C5H11 (25)] and of d,l-3,4-bis(3'-hydroxyphenyl)hexane (21) are described. In vitro these compounds inhibited the [3H]estradiol receptor interaction competitively, exhibiting Ka values between 0.20 x 10(9) (20) and 0.11 x 10(6) M-1 (24). In vivo the meso compounds reduced the estrone-stimulated mouse uterine growth; the most effective compounds were 20, 22, and 23 (53, 50, and 45% inhibition, respectively). Compounds 20 and 22-24 showed weak estrogenic activity in the mouse uterine wt test and in the vagina cornification test. Compounds 19 (NSC-297169), 20 (NSC-287170), and 22 (NSC-297171) exhibited a dose-dependent growth inhibition on the MCF-7 human breast tumor cell line (10(-6) to 10(-9) M). These compounds also showed a marked dose-dependent inhibition on the DMBA-induced, hormone-dependent mammary carcinoma of the Sprague-Dawley rat corresponding to their association constants (Author abstract) (19 Refs)

44. MAMMARY CANCER METASTASES AT THE SKULL BASE. REPORT OF TWO CASES.

Fabregat Mayor J, Rosell Costa R, Valenti Celaya JM, Tusquets Trias de Bes I, Lopez Ibanez P, Vivancos Lleida J

Servicio de Oncologia Medica, Hospital Gral. Ntra. Sra. de la Esperanza, Barcelona, Spain

Oncologia; 6(4):52-56 1981

Two premenopausal patients 37 and 43 yr old had been treated by radical mastectomy 6 mo and 5 yr previously respectively, followed in case 1 by conventional radiotherapy and in case 2 by megavoltage radiotherapy. In both cases first metastatic symptoms were visual and bone destruction at the base of the skull was revealed by radiology. The patients received combination radiotherapy (5,000 rad in 6.5 wk), polychemotherapy (adriamycin on day 1 and cyclophosphamide on days 3, 4, 5, and 6 of a 21-day cycle), and hormone therapy (medroxyprogesterone acetate on days 1, 2, 3, 4, 5, 6, 7, and 14 of the cycle). Improvement was noted in the fifth wk in case 1 and in the third wk in case 2. Complete remission lasted 12 wk and 20 wk, respectively. (7 Refs) (In SPA)

45. THE RESPONSE OF METASTATIC ADENOCARCINOMA OF THE PROSTATE TO EXOGENOUS TESTOSTERONE.

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J Urol; 126(3):372-375 1981

In a retrospective review the response of 67 patients with metastatic adenocarcinoma of the prostate to the administration of exogenous testosterone was analyzed. Among 52 patients in whom objective and/or subjective responses were evaluable 45 experienced unfavorable responses. There was prompt regression of most unfavorable responses with testosterone withdrawal. The duration of treatment required to evoke an unfavorable response was related to the clinical status of the patient. Twenty-five percent of patients with symptomatic metastases who had received no prior treatment, 36% in symptomatic remission after endocrine therapy and 94% with symptomatic relapse after endocrine therapy experienced unfavorable responses within 30 days of treatment. No patient had objective evidence of tumor regression during testosterone therapy but seven patients, six with remission and one untreated, experienced symptomatic benefit. We conclude that the response of patients with metastatic prostate cancer to exogenous testosterone is related to the mass and endocrine treatment status, and that exogenous testosterone can stimulate prostatic neoplasms that proliferate in the absence of normal endogenous testosterone levels. (Author abstract) (14 Refs)

46. PROGESTERONE TREATMENT OF RENAL CANCER.

Takesue T, Ueda T
Dept. Urology, Faculty Medicine, Kyushu Univ., Higashi-ku, Fukuoka 812, Japan
Nishinippon Hinyokika; 43(2):252-256 1981

The therapeutic effect of progesterone on renal cancer was evaluated from the following two aspects: (1) the treatment of inoperable or metastatic renal cancer and (2) the prevention of metastasis after nephrectomy. Out of 16 patients with inoperable or metastatic renal cancer, only 1 showed a substantial physical improvement after progesterone therapy. Eight patients with metastatic disease underwent nephrectomy and the three treated with progesterone had a longer mean survival time than the five control cases; 31.6 mo vs 4.6 mo. Therefore we intend to give progesterone to nephrectomized patients with metastatic renal cancer. Nine patients with low-stage renal cancer were given progesterone as long as possible after nephrectomy to prevent development of metastasis. All of them are alive without any evidence of metastasis, indicating a favorable effect of progesterone. The observation period, however, was limited to 3 yr. Further follow-up of the patients is necessary to arrive at a conclusion. (13 Refs) (In JPN)

47. PROGESTIN THERAPY FOR ADVANCED OVARIAN CANCER: A PHASE II EASTERN COOPERATIVE ONCOLOGY GROUP TRIAL.

Slayton RE, Pagano M, Creech RH
Section Medical Oncology, Dept. Internal Medicine, Rush Medical Coll., 1725 W. Harrison St., Chicago, IL, 60612
Cancer Treat Rep; 65(9):895-896 1981

Medroxyprogesterone acetate was administered to 19 patients no longer responding to surgery, radiation therapy, or conventional cytotoxic chemotherapy. Dosage was 1,000 mg im daily for 8 wk, or longer if no tumor progression was noted. Performance status was classifies as Grade 0 (fully active), Grade 1 (able to do light work), grade 2 (ambulatory, but unable to do work), Grade 3 (capable of limited self-care, confined to bed or chair), or Grade 4 (incapable of self-care, confined to bed or chair). No patients of Grade 4 were accepted. Of the patient tested there were one Grade 0, nine Grade 1, five Grade 2, and four Grade 3. Regression was defined as 50% or greater decrease in the products of the perpendicular diameters of measurable lesions. Progression was defined as 25% or greater increase over original measurements, or the appearance of new tumors. No response to treatment was noted in any case. Median survival was 2 mo, with 75% dying within 4 mo. Restriction of trial use of progestin therapy to patients with endometrioid histology is recommended. (10 Refs)

48. PRODUCTION OF OVARIAN TUMORS BY HORMONE ADMINISTRATION.

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Kurume Med J; 28(1):35-43 1981

The influence of hormone administration on tumor production was studied in female Wistar rats implanted with chemical carcinogens (9,10-dimethyl-1,2-benzathracene (DMBA), 20-methylcholanthrene, (MC), 3,4-benzpyrene (BP), or 4-nitroquinolin-N-oxide (NQO)). The hormones were an estriol preparation (EST), a progesterone preparation (PROG), a testosterone preparation (AND), a dexamethasone preparation (ACH), and human chorionic gonadotropin (HCG). The incidence of solid tumors was highest with DMBA, less with MC and lowest with BP and NQO. ACH and EST appeared to accelerate tumor growth: the incidence of solid tumors at 20 wk was not significantly different, while at 40 wk it increased to 90% in the ACH group. Up to 20 wk in the hormone-treated groups, tumor incidence was low; however, the tumor incidence increased thereafter. The highest total incidence of cystic tumor was found in the EST group, compared to controls. The solid tumors included fibromas, sarcomas, and adenocarcinomas. In the AND, PROG, and EST groups, the tumors were either fibroadenomas or fibromas. In the HCG group fibroadenomas predominated. Sarcomas appeared in the 30th and 40th wk in the controls and the EST and PROG groups, respectively. The av wt of the tumors produced by ACH and EST was greater than the control, with the largest tumor in the EST group. (27 Refs)

49. HYDROCORTISONE TEST TO STUDY THE 'RECIRCULATING' LYMPHOCYTIC POPULATION. RESEARCH IN PATIENTS WITH LYMPHOPROLIFERATIVE AND SOLID NEOPLASTIC DISEASE.

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Quad Sclavo Diagn; 17(1):1-9 1981

The hydrocortisone (OHC) test was performed in four normal controls (30-50 yr) and results compared with those from 12 patients (54-82 yr) with solid neoplasia and 20 patients (20-82 yr) with lymphoproliferative disease in different phases of clinical evolution. After fasting, 400 mg hydrocortisone was injected iv; 4 hr later the decrease of peripheral blood lymphocytes was av 66.9% (60.95-72.48%). Solid neoplasia patients had an av decrease of 55.74% (11.32-74.70%), a difference which does not appear statistically significant. The decrease was more pronounced in cases of lymphoproliferative disease with av 38.28% (11.94-68.89%), but different results were obtained for different diseases. The greatest decrease was observed in infective mononucleosis and chronic lymphatic leukemia, followed by non-Hodgkin lymphomas. (38 Refs) (In ITA)

50. THERAPEUTIC POSSIBILITIES IN PARANEOPLASTIC HYPERCALCEMIA.

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Med Welt; 32(32/33):1219-1221 1981

Hypercalcemia syndrome is a frequent complication in malignant diseases, occurring in 42% of mammary carcinomas, 12% of bronchial carcinomas, and 20% of plasmocytomas. Four pathophysiological causes are: (1) decalcification of bone by metastases, (2) osteoclast activating factor, (3) pro duction of an atypical parathormone by a tumor, and (4) synthesis of atypical prostaglandin E metabolites, which mimic parathormone. Symptoms include dehydration, polydipsia, polyuria, kidney failure, vomiting, constipation, coma, and death. Therapeutic principles are based on (1) forced renal elimination of excess calcium by diuresis, (2) medicinal control of calcium metabolism by corticosteroids, indomethacin, mithramycin, and diphosphonate, (3) and hormonal control of calcium exchange by calcitonin. Five clinical cases are reviewed. No serious therapeutic problems were encountered. (11 Refs) (In GER)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

51. HORMONAL THERAPY AND ALTERATIONS OF IMMUNITY OF PROSTATIC CANCER.

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Neoplasma; 28(3):345-350 1981

Retrospective evaluation of cell-mediated tumor-associated immunity in patients with prostatic cancer before and after the receipt of non hormonal or hormonal therapy disclosed that patients receiving hormonal therapy, ie, orchiectomy and/or estrogen, possessed significantly lower levels. The potential clinical relevancy of the suggested immunosuppressive effects of hormonal therapy on tumor-host responsiveness is considered in view of the present and previous observations. (Author abstract) (25 Refs)

GENERAL REVIEWS ON STEROID HORMONES

52. CURRENT CONCEPTS IN THE MANAGEMENT OF BREAST CANCER.

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Am Fam Physician; 24(3):119-126 1981

Patient evaluation, therapeutic options, and new developments in the treatment of primary and metastatic breast cancer are reviewed. Recent studies have demonstrated that less radical procedures may be as effective as more extensive procedures. The goals of primary treatment is to remove all obvious tumor, to obtain adequate tissue for steroid receptor analysis, and to examine the axillary contents. Axillary dissection should be performed in all patients with primary tumors. Needle biopsy is helpful for patients who are undecided about the choice of primary treatment. Primary treatment of patients with advanced disease must be individualized. Radionuclide scans may be useful in the perioperative evaluation, while tumor marker assays are not cost-effective in patients with early-stage disease or in perioperative management. Steroid receptor assays should be obtained on all primary tumors. Adjuvant therapy has generally been reserved for patients at high risk for recurrence. The use of hormonal therapy alone is controversial. Adjuvant chemotherapy may be useful in selected patients. Current therapy for advanced breast cancer is palliative; cures are rare. Complications arising in breast cancer patients include bone metastases, hyperca lcemia, CNS metastases, and spinal cord compression. Breast reconstruction is briefly discussed. (8 Refs)

53. HORMONE MANAGEMENT OF METASTASIZING CARCINOMA OF THE BREAST.

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II Clinica Chirurgica Generale, Universita di Messina, Messina, Italy
Minerva Chir; 36(12):853-860 1981

A review is made of treatment given between 1958-1978 to 448 metastatic breast cancer patients. Most metastases were localized to the bones (146 cases), lungs (85 cases), or liver (17 cases). Hormonal therapy was initiated at least 1 mo after termination of previous therapy; 102/228 patients improved (66.6% postmenopausal, 22.7% in menopause, and 10.7% premenopausal). Ovariectomy was the best therapy for premenopausal patients (48 cases): 45% improved, with av remission time 12-18 mo. Different hormones and antihormones were used with less success. Estrogen receptors were studied in 62 cases (34 with primary tumor and 28 with metastases). The receptors were present in 47% with primary tumors and in 37.5% with metastases; receptor presence was more frequent (46.2%) and at a higher level in postmenopausal cases. This test is most valuable in projecting hormone management. (43 Refs) (In ITA)

54. NEOPLASIA AND HORMONAL CONTRACEPTION.

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Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104
Clin Obstet Gynecol; 24(3):903-925 1981

The relationships between use of oral contraceptives and neoplasia are reviewed. Problems of investigation include lack of suitable animal models, lag time following exposure to carcinogens before development of overt malignancy, low incidence of malignancies in young women, and the wide range of factors influencing neoplasia. Investigative methods include case reports, disease rates and trends, case comparisons, and cohort studies. Breast disease is discussed with respect to the preclinical phase of breast cancer, breast cancer and chronic mastitis, the estradiol hypothesis, and the relationships between oral contraceptive use and benign and malignant breast disease. The relationships of oral contraceptives to liver tumors, pituitary tumors, endometrial hyperplasia, cervical neoplasia, ovarian disease, and choriocarcinoma are evaluated based on current published data. (56 Refs)

55. HORMONAL RELATIONSHIPS, RECEPTORS, TUMOUR MARKERS.

Harper ME, Chaisiri P, Slade J, Peeling WB, Griffiths K
Tenovus Inst. for Cancer Res., Welsh Natl. Sch. Medicine, Cardiff CF4 4XN, Wales
Recent Results Cancer Res; 78:44-59 1981

The endocrine factors concerned with the etiology of cancer of the prostate are unclear. Hormones and glands that could be concerned in controlling the growth and function of the prostate gland include testosterone, adrenal androgens, sex hormone-binding globulin, prolactin, and others. The rela tionship between hormone concentrations in the plasma of patients with proven prostatic cancer and various clinical parameters was investigated. While promotion of prostatic neoplasia may be dependent on some particular, abnormal endocrine status of certain individuals, it will be difficult to identify a high-risk group from simple plasma analysis of hormones. Radioimmunoassays for salivary steroids might allow a more detailed study of the chrono-endocrinology relating to aging and prostate cancer. The value of androgen receptor assays in human prostatic carcinoma as a predictor of endocrine response has not yet been established. It is possible that an increased responsiveness to normal hormone levels in plasma may be caused by biochemical changes within the prostatic cells. The use of polyamines and acid phosphatase as tumor markers is discussed. Spermine and spermidine levels did not relate to primary tumor staging or the metastatic status of the patient, and their values were of little value in detecting or in monitoring response to therapy. Serum acid phosphatase activity is elevated in patients with prostatic carcinoma, 65-90% of patients with bone metastases, and 5-10% of those with clinically demonstrable metastatic cancer. The prostatic portion of acid phosphatase must be defined. An immunoassay for that purpose is described. (65 Refs)

56. ENDOCRINE AND CYTOXIC THERAPY.

Smith PH
Dept. Urology, St. James's Univ. Hosp., Leeds, England
Recent Results Cancer Res; 78:154-172 1981

Three major systems of clinical classification of prostatic cancer are reviewed: (1) Veterans Administration Cooperative Research Group (VACURG); (2) American Urological Association (AUA), and (3) Union International Contre le Cancer (the TNM system: tumor, node, metastases). The contribution of the VACURG to hormone therapy of prostatic cancer is reviewed. Alternative therapy may involve the use of estrogens, progestogens, anti-androgens, and medical adrenalectomy. A recognized pattern of trials, each of increasing complexity, is outlined. Activities of the European Organization for Research on the Treatment of Cancer Urological Group are reviewed. Problems in evaluating the remission in prostatic cancer are discussed. The National Prostatic Cancer Project has conducted clinical studies on cytotoxic agents in prostatic cancer: symptomatic relief and survival prolongation have been demonstrated, although further results are needed to fully assess the effect of cytotoxic agents. (41 Refs)

57. GROWTH KINETICS.

Alison MR, Wright NA
Dept. Histopathology, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 OHS, England
Recent Results Cancer Res; 78:29-43 1981

Since direct estimates of growth rate of prostate cancer (PC) are unfeasible in humans, the respective roles of cell production and cell loss in determining overall tumor growth rates can only be speculative. The mitotic rate and thymidine labeling, DNA analysis of cells in tumors, studies in culture, and experimental prostatic tumors are each discussed.The mitotic index data suggest that some of the more poorly differentiated tumor types have higher cell production rates than the majority of moderately to well-differentiated tumors. Most experimental tumors grow faster than those in man. The slow growth rate of human tumors indicates the presence of important growth restraints. Mitotic Rate and thymidine labeling and studies in tissue culture of benign prostatic hyperplasia are discussed. Androgens and the cell cycle are discussed with respect to the growth fraction, stimulated DNA synthesis, and some properties of stimulated cells. In populations with a low proliferative rate it may be difficult to distinguish between cells slowly progressing through the division sequenee and those cells actually arrested or resting in a separate phase (G0). Evidence is presented that most cells in prostatic tissues are in a state of proliferative rest (G0), an that increased cell production is achieved by actively promoting G0 cells into the division sequence. (49 Refs)

OTHER RELATED STUDIES

58. GRANULOSA THECA CELL TUMORS IN PREMENARCHAL GIRLS: A CLINICAL AND PATHOLOGIC STUDY OF TEN CASES.

Lack EE, Perez-Atayde AR, Murthy AS, Goldstein DP, Crigler JF, Vawter GF

Dept. Pathology, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA, 02115

Cancer; 48(8):1846-1854 1981

Granulosa theca cell tumor (GTCT) in the premenarche accounted for 7% of all ovarian tumors treated at the Children's Hospital Medical Center from 1928 through 1979. The av age of the 10 girls at the time of diagnosis was 5 yr (range 11 mo-12 1/2 yr) with precocious 'pseudopuberty' and an abdominal mass being the most common presentation. GTCTs were solitary (5 right, 5 left) with an av diameter of 12.1 cm. Histologic examination showed a predominantly diffuse or solid pattern with prominent luteinization; Call-Exner bodies and folded ('coffee-bean') nuclei were inconspicuous. Ultrastructural examination of one GTCT confirmed the presence of both granulosa and theca components with the latter showing extensive luteinization; estradiol, testosterone and prolactin were demonstrated in the same tumor using immunologic techniques. The av follow-up time was 21 yr with 9 of the 10 patients being followed for more than 10 yr. Salpingo-oophorectomy resulted in cures despite the occurrence of tumor spillage in two patients. The prognosis for GTCTs in the premenarche appears more favorable than for those occurring in adulthood, but further study is needed to completely define their full biologic potential; the significance of subsequent breast canc er in two long-term survivors merits further investigation as well. (Author abstract) (24 Refs)

59. LONG-TERM FOLLOW-UP OF OVARIAN FUNCTION IN WOMEN TREATED WITH MOPP CHEMOTHERAPY FOR HODGKIN'S DISEASE.

Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT
Building 10, Room 12N226, Bethesda, MD, 20205
Am J Med; 71(4):552-556 1981

Twenty-seven women previously treated with MOPP (mechlorethamine, vincristine, procarbazine, prednisone) chemotherapy were evaluated to determine the status of ovarian function. All patients had completed therapy a median of 9 yr earlier and had a median age of 30 yr at the time of evaluation. Persistent amenorrhea has occurred in 11 of 24 patients (46%) treated with MOPP alone or MOPP plus radiation excluding the pelvis. Of patients with amenorrhea, 89% were older than age 25 at the time of treatment. In contrast, 80% of patients younger than age 25 at treatment continue to menstruate regularly. The time from diagnosis to amenorrhea was significantly shorter in the older patients (p = 0.001). Evaluation of serum gonadotropin and estradiol levels confirms ovarian failure as the cause of amenorrhea in all patients. Overall, these 27 patients have borne 13 normal children subsequent to chemotherapy. This long-term follow-up study demonstrates that chemotherapy-induced ovarian failure is age-related, that ovarian failure is often gradual in onset following the completion of chemotherapy and that, to date, the children born of women treated with this chemotherapy regimen appear to be entirely normal. (Author abstract) (17 Refs)

60. CUSHING'S SYNDROME: GENERAL AND SPECIAL DIAGNOSTICS.

Tenschert W, Vetter W, Fischer M, Siebenschein R, Studer A, Holland-Cunz B, Siegenthaler-Zuber G, Vetter H
Medizinische Universitats-Poliklinik Munster, Universitatsspital Zurich, Zurich, Switzerland
Dtsch Med Wochenschr; 106(38):1213-1216 1981

Over a 5-yr period 37 patients (28 women, 9 men) with Cushing's disease were studied. Hypophyseal-hypothalamic disregulation was present in 24 (mean age 33.8 yr), adrenal adenoma in 8 (mean age 37.1 yr), and adrenal carcinoma in 4 (mean age 54.8 yr). One patient (aged 29 yr) had Cushing's syndrome due to an ectopic ACTH overproduction in Zollinger-Ellison syndrome. Arterial hypertension was present in 31 patients. Under basal conditions the urinary excretion rate of free cortisol was evaluated in all but one of 127 specimens from the 37 patients. Levels of 17-hydroxysteroids (17-OH-CS) were above normal in only 59% (77 specimens from the 37 patients). Suppression tests with 2 mg and (or) 8 mg dexamethasone indicated marked inhibition of cortisol excretion (on measuring both free cortisol and 17-OH-CS) only in the patients with hypophyseal-hypothalamic disregulation. Plasma ACTH Values, measured in 7 of the 24 patients with central Cushing's syndrome, had a mean value of 810 pg/ml (normal up to 60 pg/ml). A Nelson syndrome developed after bilateral adrenalectomy in four patients with central Cushing's syndrome. 131I-cholesterol scan in 13 patients revealed marked bilateral increase in uptake of radioactivity in the adrenal region of five patients with hypophyseal-hypothalamic disregulation, while unilateral increased uptake was observed in the four patients with adrenal adenoma. There was no or only little activity increase in the four patients with adrenal carcinoma. The results indicate that hypercorticism can be more reliably diagnosed by measuring urinary excretion of free cortisol rather than of 17-OH-CS. The dexamethasone inhibition test (with 2 and/or 8 mg dexamethasone) indicates definite suppression of hormone excretion rates in central Cushing's syndrome. The 131I-cholesterol scan is of limited value in the diagnosis of adrenal carcinoma. (Author abstract) (no Refs) (In GER)

61. CORTICOSTERONE AND GLUCOCORTICOID-BINDING FUNCTION OF TRANSCORTINE AFTER LOW DOSE SINGLE AND FRACTIONATED IRRADIATION.

Dudina TV
Inst. Physiology, Minsk, USSR
Radiobiologiia; 21(3):413-417 1981

The effect of a single and fractionated irradiation (40 and 50 R) on the hypothalamus-pituitary-adrenal cortex system was studied in Wistar rats. The early changes in the level of total and free corticosterone and in the glucocorticoid-binding function of transcortine indicated a stimulation of the adrenal cortex function. Normalization of the glucocorticoid function of the adrenals was recorded within the first mo after single irradiation, on day 60 after 2-wk fractionated irradiation, and on day 180 after 10-wk fractionated irradiation. (8 Refs) (In RUS)

62. RESULTS OF THE ITALIAN INTERLABORATORY QUALITY CONTROL PROGRAM FOR ESTRADIOL RECEPTOR ASSAY.

Fumero S, Berruto GP, Pelizzola D, Grilli S, Buttazzi C, Di Fronzo G, Ronchi E, Bozzetti C, Mori P, Concolino G, Marocchi A, Della Cuna GR, Ziebera C, Cerrutti G, Ros A, Piffanelli A
(c/o Piffanelli), Instituto di Radiologia dell'Universita, Corso Giovecca n. 203, 44100 Ferrara, Italia
Tumori; 67(4):301-306 1981

This article presents results of the first Italian quality control program for determining the estradiol receptor on lyophilized guinea pig and calf uteri. Despite considerable variability in quantitative terms, the results concur in ability to define samples as positive or negative for receptor content. One of the parameters that most strongly influences accuracy of determination of receptor concentration is protein assay. The evaluation of several lyophilized preparations at scalar concentrations permitted identification, by linear regression, for each laboratory of the systemic and non-systemic variables. More comparable results will be forthcoming when a standardized methodology program has been fully adopted. (Author abstract) (20 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. GLUCOCORTICOID-SUPPRESSIBLE HYPERALDOSTERONISM: A CLUE TO THE MISSING HORMONE?

Mulrow PJ
Medical Coll. Ohio, Toledo, OH, 43699
N Engl J Med; 305(17):1012-1014 1981

The differential diagnosis of aldosterone-producing adenoma, idiopathic hyperaldosteronism, and glucocorticoid-suppressible hyperaldosteronism (GSH) in patients with primary aldosteronism is described. Possible etiology of suppression of aldosterone production by glucocorticoids in GSH is discussed. The roles of ACTH and beta-lipoprotein in GSH are considered. (11 Refs)

2. RELATION BETWEEN ADRENAL FUNCTION AND 7,12-DIMETHYLBENZ[A]-ANTHRACENE-INDUCED MAMMARY CANCER OF THE RAT.

Nakamura Y, Kodama M, Kodama T
Dept. Surgery, Inst. Balneotherapeutics, Kyushu Univ., 4546 Tsurumihara, Beppu 874, Japan
Gan; 72(5):679-683 1981

The excretions of urinary steroids were investigated in rats in the course of mammary carcinogenesis by 7,12-dimethylbenz[a]anthracene (DMBA). The carcinogen was fed to female Sprague-Dawley rats on days 50 and 64 after birth at a dose of 10 mg each. The excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), increased temporarily (at 80 days of age) in DMBA-treated rats as compared with non-treated controls. The excretion of adrenal corticosteroid, 17-deoxy-corticosteroid (17-DOCS), was lower than normal in the rats that failed to develop tumors within 200 days after receiving DMBA. The difference between the above non-responders and the tumor-developing responders (or the non-treated controls) was significant at 80 and 120 days of age, but not at 160 days of age. The final tumors wt at 160 days of age were also positively correlated to the excretion of 17-DOCS at 130 days of age. It was indicated that the overall process of DMBA carcinogenesis could be promoted by the endogenous adrenocortical steroids. The possible mechanism underlying the production of mammary cancer is discussed in the light of the metabolic intimacy between DMBA and the adrenal steroids. (Author abstract) (17 Refs)

3. IN VITRO INHIBITION OF STEROIDOGENETIC ENZYME ACTIVITY BY A NEW STEROID INHIBITOR 'TRILOSTANE'.

Ojima M, Sasano N
Dept. Pathology, Tohoku Univ. Sch. Medicine, Sendai 980, Japan
Nippon Naibunpi Gakkai Zasshi; 57(7):997-1008 1981

In vitro effects of trilostane (TR: 4-alpha-5-epoxy-17beta-hydroxy-3-oxo-5-alpha-androstane 2alpha-carbonitril) on steroid production and conversion of tritiated pregnenolone to other steroids in the adrenal glands were investigated. Samples of adrenocortical tissue were obtained from normal adrenals in 32 cows and 1 patient with breast cancer, from 2 adenomas and 1 hyperplasia from 3 patients with Cushing's syndrome, from an adenoma in a patient with primary aldosteronism, and from an adrenal carcinoma associated with hypermineralocorticoidism. Ratios and production of steroids were determined with thin layer chromatography, a liquid scintillation counter, and/or radioimmunoassay. Conversion of tritiated pregnenolone to other steroids was reduced with 2 x 10(-8) M and 2 x 10(-7) M TR in the beef adrenal gland, indicating that TR effectively inhibited the 3beta-hydroxysteroid dehydrogenase system. Addition of 2 x 10(-7) M TR to incubation mediums markedly reduced the conversion of pregnenolone to other steroids in the adrenal adenoma in the patients with Cushing's disease and reduced in vitro production of progesterone, 11-deoxycorticosterone, 17alpha-hydroxyprogesterone, and cortisol by tissue from normal adrenal cortex, aldosteronoma, and adrenal carcinoma associated with hypermineralocorticoidism. TR was shown to markedly reduce the production of 17alpha-hydroxypregnenolone and 17alpha-hydroxyprogesterone production in humans, suggesting its inhibiting effects on the 17 alpha-hydroxylase system. (7 Refs) (In JPN)

4. STEROID METABOLISM AND OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

Miller WR, Hawkins RA, Forrest AP
Dept. Clinical Surgery, Univ. Edinburgh, Edinburgh, Scotland
Eur J Cancer Clin Oncol; 17(8):913-917 1981

Metabolism of 7alpha[3H] testosterone and estrogen receptor activity have been measured in 54 human breast cancers. All tumors converted testosterone to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol, but unequivocal evidence for production of estradiol was obtained in only 29 of the tumors. Thirty-seven tumors were classified as estrogen receptor 'positive' containing levels in excess of 5 fmol/mg cytosol protein. Although mean conversions to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol were all higher in estrogen receptor negative tumors as compared with receptor positive group, the differences did not reach statistical significance. There was, however, a significant trend for estradiol synthesis to be associated with estrogen receptor positive tumors (p less than 0.025). All tumors with very high level of receptors converted testosterone to estradiol. (Author abstract) (21 Refs)

5. IN VIVO ANALYSIS OF UV-B FORMATION OF 5-6 ALPHA EPOXY CHOLESTEROL (MEETING ABSTRACT).

Krinsky NI
Tufts University School of Medicine, Boston, MA
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

To identify types of photooxidations initiated by UV-B in vivo, the cholesterol oxidation products formed when mice are irradiated with UV-B have been analyzed. Several compounds also have been prepared from 14C-cholesterol to serve as internal standards. Preliminary results indicate that cholesterol is the major radioactive skin steroid observed one hr after ip administration of mevalonic acid (MVA), with smaller amounts of two other radioactive compounds not yet firmly identified. For animals exposed to UV-B, increased amounts and types of more polar radioactive peaks have been found. Some observed changes may be due to UV-B catalyzed formation of vitamin D3 from 7-dehydrocholesterol. When cholesterol undergoes a Type I photooxidation, analogous to a radical oxidation, it forms the epimeric cholesterol 7-hyperoxides as well as the epimeric cholest-5-ene-3beta, 7-diols. In contradistinction, when cholesterol is oxidized by electronically excited (singlet) molecular oxygen in a Type II photooxidation, the initial product is 3beta-hydroxy-5-alpha cholest-6-ene-5-hydroperoxide. These compounds can be isolated and separated by thin-layer chromatography (TLC), by gas-liquid chromatography (GLC) and should be amenable to separation by high-performance liquid chromatography (HPLC). For max sensitivity, cholesterol labeled with either tritium (3H) or radioactive carbon (14C) will be utilized. The labeling will be carried out in vitro, using labeled mevalonic acid as a specific precursor of tissue cholesterol. Because mevalonic acid goes exclusively to steroids, this procedure avoids having large amounts of nonspecific radioactivity distributed through the tissues. Through the use of endogenous labeled cholesterol, the initial pathway of photooxidation induced by UV-B should be amenable to elucidation. Simultaneously, the formation of the carcinogen, cholesterol-5alpha, 6alpha epoxide will be followd by TLC and GLC and HPLC and attempts will be made to obtain precursor-product relationships in order to determine the immediate precursor of this compound. (no Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

6. ANOMALOUS POSTURAL ALDOSTERONE RESPONSE IN GLUCOCORTICOID-SUPPRESSIBLE HYPERALDOSTERONISM.

Ganguly A, Grim CE, Weinberger MH
Indiana Univ. Medical Center, Clinical Building-477, 1100 W. Michigan St., Indianapolis, IN, 46223
N Engl J Med; 305(17):991-993 1981

An anomalous fall in plasma aldosterone was reported for 5/6 patients in whom glucocorticoid treatment completely reversed hypertension and biochemical abnormalities. Thus, the syndrome of glucocorticoid-suppressible hyperaldosteronism (GSH), in addition to that of aldosterone-producing adenomas (APA), is manifested by this anomalous response. In normal persons the plasma aldosterone concentration rises with assumption of upright position, while in GSH and APA patients a paradoxical response is observed. (20 Refs)

7. HYPERENINEMIC HYPOALDOSTERONISM IN ASSOCIATION WITH NEOPLASIA INDUCED HYPERCALCEMIA IN THE FISCHER RAT.

Sowers JR, Sollars E, Nyby MD, Jasberg K, Tuck ML
Endocrine Metabolism Div. (111E), Veterans Admin. Medical Center, 16111 Plummer St., Sepulveda, CA, 91343
Metabolism; 30(10):987-991 1981

Alterations in the renin-angiotensin-adolosterone system in hypertensive, hypercalcemic Fischer rats bearing transplanted Leydig cell tumors were evaluated by measuring plasma aldosterone (PA), plasma renin activity (PRA), and systolic blood pressure (BP) responses to immobilization stress. PA and plasma corticosterone responses to graded ATCH infusions and PA and BP responses to graded angiotensin II (AII) were also evaluated. The results demonstrated marked increases in basal PRA that correlated with the degree of hypercalcemia reached after tumor transplanation. Postive correlations between serum calcium and PRA suggested that increased calcium ion stimulated renin secretion. PRA responses to immobilization stress were increased in tumor-bearing rats. However, basal PA and corticosterone levels were decreased in hypercalcemic rats, as were PA and corticosterone responses to ACTH and PA responsess to immobilization stress and AII. BP responses to immobilization stress and AII correlated positively with serum calcium concentrations. The possibility that the hypertension in these rats was related to a vasoconstrictor effect of calcium on peripheral blood vessels is discussed. (28 Refs)

8. LABORATORY DIFFERENTIAL DIAGNOSIS BETWEEN CUSHING'S SYNDROME AND SIMPLE OBESITY.

Zhang G, Meng X, Yang W, Wu C, Gao S, Guo Z
Dept. Endocrinology, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Yixue Zazhi; 61(3):155-158 1981

Differential diagnosis is described for 43 cases of surgically proven Cushings' syndrome (7 males, 5 females) and 58 cases of simple obesity (7 males, 51 females). Among the patients with Cushing's syndrome, pathological diagnosis of hyperplasia were made in 26 cases (5 males, 21 females), adenoma in 14 cases (2 males, 12 females) and adenocarcinoma in 3 cases (all females). Patients were tested for 24-hr urinary corticosteroids and total plasma cortisol contents at 8 am, 5 pm and midnight. Overnight dexamethasone suppression test (ODST) was also used. Results showed that urinary free cortisol (UFC) and 17-OHCS were much higher in Cushing's syndrome patients than in simple obesity. Total plasma cortisol content was also higher in Cushing's syndrome than in simple obesity at all the times tested, showing the biggest difference (7.8 times) at midnight. The ODST was found useful in the differentiation between tumor and hyperplasia while 17-OHCS and UFC had no value in this respect. It was concluded that total plasma cortisol at midnight and UFC are useful in the differential diagnosis between Crushing's syndrome and simple obesity. (4 Refs) (In CHI)

9. AN UNUSUAL CASE OF PRIMARY ALDOSTERONISM DUE TO ADRENAL ADENOMA AND WITH ELEVATED PLASMA RENIN ACTIVITY (MEETING ABSTRACT).

Mittelstaedt GV, Vecsei P, Hackenthal E, Georgi M, Haack D, Filser T, LichtwaldK
Klinikum Mannheim, Mannheim, W. Germany
Acta Endocrinol [Suppl]; 96(240):57 1981

A 46-yr-old female patient with hypertension and low normal serum potassium showed elevated plasma aldosterone concentrations and also elevated plasma renin activities (PRA). The aldosterone concentrations were: 25.1/111.4; 52.2/137.5; 46.1/84.6 ng/100 ml. The corresponding PRA were: 5 .0/9.2; 7.8/12.4; 3.4/6.2 ng angiotensin/ml/60 min. The first value was obtained in supine position, the second one after 30 min orthostasis. The normal ranges for aldosterone are 2-10/5-25 ng/100 ml and for PRA 0.3-2.0/0.5-4.0 ng angiotensin/ml/60 min. The plasma cortisol and urinary cortisol metabolites were found normal. Plasma corticosterone was periodically elevated: 1.29; 2.30; 6.64; 5.54; 1.60 ug/100 ml. The plasma deoxycholate was elevated: 136.9; 101.8 ng/100 ml. Unexpectedly, urinary aldosterone-18-glucuronide, free aldosterone and free 18-OH-corticosterone were in the normal range. The catecholamines were also within the normal range. Sonography, isotope nephrography, iv pyelography as well as blood and urine analyses, and the renal venous PRA-quotient did not indicate renal involvement. However, an adrenal adenoma (left side) could be established by computer tomography and phlebography. In the right adrenal venous plasma aldosterone concentration was 930 ng/100ml, in the left one 17,000 ng/100 ml. After removal of the adrenal adenoma, blood pressure, plasma aldosterone, and PRA normalized: 130/90, 120/80 mmHg blood pressure; 9.9/13.7; 4.5/7.1 ng/100 ml plasma aldosterone concentration; 1.7/3.8; 1.1/2.0 ng angiotensin/ml/60 min PRA. This case shows that elevated PRA cannot exclude hypertension with hyperaldosteronism due to an adrenal tumor. The mechanism of the elevation of the PRA is still unknown. (no Refs)

10. ACTH AND CORTISOL PATTERNS AFTER SELECTIVE ADENOMECTOMY IN CUSHING'S DISEASE (MEETING ABSTRACT).

Ludecke DK, Muchler HC, Caselitz J, Saeger W
Neurochirurgische Abteilung, Marienkrankenhaus, Hamburg, W. Germany
Acta Endocrinol [Suppl]; 96(240):61 1981

The occurrence of a period of subnormal ACTH and cortisol secretion after selective adenomectomy in Cushing's disease (CD) has been reported previously. To further elucidate immediate postoperative secretory patterns in relation to follow-ups, perioperative plasma samples were analyzed in 19 patients with CD. Cortisol was measured by commercial radioimmunoassay and ACTH by RIA after plasma extraction according to Muller et al. After total transnasal removal of the adenoma an exponential decline of ACTH and cortisol plasma levels was observed in all patients. In two patients cortisol replacement was started too early overlapping the decline of endogenous cortisol secretion. In the last 8 consecutive patients corticoids were given whenever cortisol measurements indicated subnormal plasma levels, which occurred mostly within 20 hr postoperatively. During several hr of low cortisol levels no clinical problems were observed under close control in the intensive care unit. From 17 adequately followed patients, 13 showed a decrease of cortisol levels into the subnormal range. The time course was highly variable, ranging from 6-24 hr. All these pati ents with a postoperative period of ACTH and cortisol insufficiency were clinically cured. The other pituitary functions were mostly intact, whereas insufficiency for ACTH and cortisol secretion lasted up to 3 yr. Four exceptions to the regular pattern of cortisol decrease have to be described. One patient with persistent ACTH hypersecretion was cured after additional radiation therapy. In one patient normalization of ACTH and cortisol levels was followed by a relapse within 6 mo. A tumor remnant of 1 mm in diameter close to the carotid artery was detected on autopsy after the patient had died from complications following adrenalectomy. In two other postoperatively normalized patients the follow-up is inadequate. These findings suggest that a period of subnormal ACTH and cortisol plasma levels seems to be the most valid criterion of a total removal of pituitary adenomas in Cushing's disease. (3 Refs)

11. REMISSION OF CUSHING'S SYNDROME WITH HYPERSECRETION OF ACTH AND PROLACTIN DURING BROMOCRIPTINE THERAPY (MEETING ABSTRACT).

Winkelmann W, Allolio B, Heesen D, Hipp FX, Mies R
Innere Medizin II der Universitat Koln, Koln, W. Germany
Acta Endocrinol [Suppl]; 96(240):62 1981

In patients with pituitary tumors, hypersecretion of 2 or 3 pituitary hormones has occasionally been observed. The combination of hypersecretion of ACTH with growth hormone (GH) and/or prolactin (PRL) is extremely rare. In patients with Cushing's syndrome (CS) a test dose of bromocriptine (Br) is followed by a drop in plasma ACTH, whereas long-term application has no effect. Long-term suppression of ACTH by Br was also lacking in a patient with hypersecretion of ACTH, GH, and PRL. The following case report concerns a 46-yr-old male patient with CS due to a pituitary tumor with hypersecretion of ACTH and PRL. By x-ray tomography a microadenoma was recognized at the bottom of the sella turcica. Cortisol (F) and pituitary hormones were measured by radioimmunoassay. Both urinary and plasma F were found to be elevated. Plasma ACTH also was elevated. Dexamethasone failed to suppress plasma F which increased during ACTH or lysine-vasopressin administration. A test dose of Br led to a strong decrease of PRL, ACTH, and F. We therefore started a continuous therapy with Br going on until now for about 8 mo. Plasma PRL, as well as ACTH and F were already normalized 10 wk after starting the therapy. The max doses of 15 mg Br could be reduced to 7.5 mg/day very soon. Normalization of adrenal regulation was demonstrated by an effective dexamethasone suppression of plasma F and a sufficient F increase during insulin-induced hypoglycemia. At no time was hormonal replacement therapy necessary. Within 4-6 mo a clinically complete remission of CS was obvious. Since hypersecretion of ACTH and PRL was stopped by a dopamine agonist a disturb ance of dopaminergic neurotransmission seems to be involved in the pathogenesis of this case. Although the combined hypersecretion of ACTH and PRL in CS is extremely rare, the effect of Br observed in our patient should suggest measurement of PRL in all cases of central CS. (2 Refs)

12. SINGLE DOSE METYRAPONE TEST USING PLASMA 11-DEOXYCORTISOL RESPONSE AS INDICATOR IN PATIENTS WITH PROSTATIC CANCER.

Ohashi T, Morioka M, Akaeda T, Mitsuhata N, Takeda K, Ohmori H
Dept. Urology, Okayama Univ. Sch. Medicine, Okayama, Japan
Nippon Naibunpi Gakkai Zasshi; 57(7):983-996 1981

Plasma 11-deoxycortisol (S), cortisol (F), and ACTH responses to metyrapone were investigated in 13 normal adult males (21-80 yr old) and 39 with prostatic carcinoma. S was measured with a radioimmunoassay using an antiserum prepared by immunizing house rabbits with S-21 hemisuccinate bovine serum albumin and S-3-oxime bovine serum albumin. The patients were treated with diethylstilbestrol-diphosphate (10), hexestrol (1), ethynyl estradiol (1), estramustine phosphate (8), or two other agents (19). In the patients given metyrapone during estrogen therapy, both basal levels and response levels of S and F increased notably, but levels of ACTH remained within normal ranges. Compared to the controls, response levels of S, F, and ACTH in the patients treated with estrogen were unchanged 2-4 wk after discontinuation of estrogen therapy, suggesting that estrogens had no inhibitory effect on the pituitary-adrenal axis. On the other hand, the response levels of S and ACTH in the patients treated with progestational agents for a long time decreased slightly but returned to normal ranges 2-4 wk after termination of therapy, suggesting that inhibitory effects of progestational agents on the pituitary-adrenal axis was mild and reversible. (25 Refs) (In JPN)

13. LONG-TERM FOLLOW-UP OF PLASMA TESTOSTERONE LEVELS IN PATIENTS WITH PROSTATIC CANCER TREATED WITH HORMONES.

Hajek J, Hanselova M, Vrubel F
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Vnitr Lek; 27(9):852-860 1981

The plasma testosterone level was monitored in 60 patients (51-80 yr old) with histologically confirmed prostate carcinoma (Stages T2 and T3) for 1 yr during hormone treatment according to three different protocols. Twenty healthy men (10 in the age bracket 25-50 yr and 10 in the age bracket 51-80 yr) served as controls. Twenty patients (Group I) was treated with Agostilben (2 x 0.5 mg/day po), 25 patients (Group II) with Difostilben (DS: 3 x 100 mg/day po), and 15 patients (Group III) with Estradurin (80 mg/mo for 3 mo, then 40 mg/mo). Considerable reduction of the plasma testosterone level was seen approx 3 mo from the beginning of the treatment compared with the initial level and with the controls . The suppression of the testosterone level was efficient with Estradurin and DS, which reduced the testosterone levels to approx 4-5 moles/liter during the entire observation period, while the testosterone level in Group I reached a minimum at approx 7 moles/liter during mo 4 to increase to almost 10 moles/liter by the end of the observation period. Yet, the long-term administration of DS is considered risky despite the good suppressive effect. (31 Refs) (In CZE)

14. VIRILIZATION OF A POST-MENOPAUSAL WOMAN BY A TESTOSTERONE-SECRETING LEYDIG CELL TYPE ADRENAL ADENOMA.

Trost BN, Koenig MP, Zimmermann A, Zachmann M, Muller J
Dept. Medicine, Kantonsspital, CH-6004 Lucerne, Switzerland
Acta Endocrinol (Copenh); 98(2):274-282 1981

In a 60 yr old virilized woman the plasma testosterone concentration was markedly elevated, whereas the plasma cortisol and ACTH as well as urinary 17-ketosteroids, 17-hydroxycorticoids, pregnanetriol and dehydroepiandrosterone were normal. The plasma levels of LH and FSH were in the post-menopausal range. Dexamethasone suppressed the urinary 17-ketosteroids, 17-hydroxycorticoids and pregnanetriol normally, but had no effect upon the plasma testosterone. These findings led to the tentative diagnosis of an ovarian hilus cell tumor. However, bilateral oophorectomy revealed bilateral hyperthecosis without a tumor and did not result in any decrease of the plasma testosterone level. An attempt of adrenal vein catheterization succeeded only on the left side. The lack of a gradient in the testosterone concentration between blood from the left adrenal vein and a peripheral vein prompted a surgical exploration of the right adrenal gland, which led to the discovery and removal of an encapsulated Leydig cell type adenoma, characterized by Reinke's crystalloids. A testosterone concentration gradient between right adrenal and peripheral venous blood obtained intra-operatively, rapid normalization of the plasma testosterone concentration post-operatively, results of a tumor incubation study as well as the clinical outcome proved that this adenoma had been the source of the excessive androgen. A history of a late menarche and persistent menstrual irregularities together with elevated gonadotrophins in spite of excessive testosterone pointed in the possibility of a long-standing gonadotrophin-dependent gonadal cell population in the adrenal, which was fully activated only by the menopausal gonadotrophin rise. (Author abstract) (35 Refs)

15. RADIOIMMUNOASSAY OF TISSUE STEROIDS IN ADENOCARCINOMA OF THE PROSTATE.

Belis JA, Tarry WF
Dept. Urology, West Virginia Univ., Morgantown, WV, 26506
Cancer; 48(11):2416-2419 1981

Tissue steroid levels in 48 needle-biopsy samples of adenocarcinoma of the prostate were quantified by radioimmunoassay (RIA). Tissue levels of dihydrotestosterone (DHT), estradiol-17 beta, and estrone were correlated with tumor stage, histologic grade, and patient response to endocrine therapy. All patients with well-differentiated carcinoma of the prostate had tissue DHT content greater than 2.0 ng/g while 35% of patients with moderately differentiated or poorly differentiated tumors had tissue DHT content less than 2.0 ng/g. DHT content appeared to be unrelated to tumor stage. Estradiol and estrone content correlated well with tumor grade but not with tumor stage. DHT levels were measured in 17 patients with symptomatic Stage D2 carcinoma of the prostate. Thirteen patients with DHT content greater than 2.0 ng/g initially had an objective and/or subjective response to endocrine therapy. Four patients with tissue DHT levels below 2.0 ng/g had no response to hormonal therapy. Quantification of tissue DHT content by RIA is a promising method for predicting initial response to hormonal therapy in adenocarcinoma of the prostate. (Author abstract) (16 Refs)

16. STEROID SECRETION AND TESTOSTERONE BINDING IN A WOMAN WITH AN OVARIAN HILUS CELL TUMOR AND THYROTOXICOSIS.

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Am J Obstet Gynecol; 141(5):535-538 1981

Presented is the case of a 21-yr-old woman with an ovarian hilus cell tumor and thyrotoxicosis. Despite massively elevated levels of serum testosterone, virilization was lacking and cyclic ovulatory menses were maintained. Hypersecretion of thyroxine and an increased circulating testosterone-estradiol globulin (TeBG) resulted in a level of free testosterone lower than expected, thereby perhaps accounting for the negligible androgen effect. Determinations of peripheral and ovarian venous steroids provided the first in vivo evidence for the preferred synthesis of testosterone via the delta5 pathway in a hilus cell tumor. (Author abstract) (13 Refs)

17. PITUITARY-OVARIAN HORMONES AFTER LOW-DOSE ENDOMETRIAL AFTERLOADING IRRADIATION.

Gronroos M, Kauppila O, Pulkkinen M, Turunen S, Salmi T, Raekallio J

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Int J Gynaecol Obstet; 19(5):375-380 1981

Immediate and long-term effects of low-dose endometrial irradiation on hormonal function of the pituitary-ovarian axis in 19 patients (13: 13-26 yr old, 6: 34-44 yr old) were studied. All 19 patients were mentally retarded and had been sent to the hospital for termination of menstrual bleeding via intrauterine irradiation. During the 10-mo follow-up period, av plasma estradiol (E2) levels did not change, follicle-stimulating hormone concentration increased, and plasma progesterone (P) levels, low prior to treatment, remained low (less than 5 nanomole (nmol)/liter). However, high P levels (15-34 nmol/liter) were observed in 3/19 patients during the later 2-9 yr follow-up period. In the 2-9 yr after treatment, plasma E2 levels were significantly higher than those of healthy postmenopausal women and did not differ from E2 levels of healthy women at days 6-7 of the menstrual cycle. Estrone (E1) levels during the later follow-up did not differ from either those of healthy women at days 6-7 of the menstrual cycle or from postmenopausal values. E1 and E2 levels were lower than those at days 12-14 of the menstrual cycle. Implications of these findings are discussed. (7 Refs)

18. TESTOSTERONE SECRETING ADRENAL CORTICAL ADENOMAS.

Imperato-McGinley J, Young IS, Huang T, Dreyfus JC, Reckler JM, Peterson RE
Cornell Univ. Medical Coll., 1300 York Ave., New York, NY, 10021
Int J Gynaecol Obstet; 19(5):421-428 1981

Hormonal data on two cases of adrenal testosterone secreting tumors are presented. Current knowledge of both clinical and hormonal features of the syndrome are summarized. A 49-yr-old postmenopausal woman presented with a 6-mo history of hirsutism and increased lethargy. Plasma testosterone (T) was 215 nanog/deciliter (ng/dl). Total hysterectomy and bilateral salpingoophorectomy were performed. Both ovaries were normal in size and showed stromal hyperplasia. No palpable suprarenal masses were observed. One wk postoperatively, plasma T level was 185 ng/dl. Eight mo later, plasma T was 670 ng/dl. Bilateral adrenal venograms showed a large mass in the left adrenal gland. Following surgical removal of a 100 g, 7.5 cm well-encapsulated adrenal adenoma, the plasma and urinary steroid levels returned to normal. A 55-yr-old postmenopausal woman was admitted to the hospital with a 3-yr history of hirsutism, progressive loss of scalp hair, and increased libido. T was the only peripheral plasma steroid found to be elevated, although plasma estradiol was slightly increased for an ovariectomized woman. Right adrenalectomy was performed and a 2.2 cm reddish-brown adenoma was found. Postoperative plasma T was 2 ng/dl. Diagnosis of this lesion is discussed. (34 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

19. MANAGEMENT OF LOCALLY ADVANCED AND DISSEMINATED BREAST CANCER.

Carter SK, Rubens RD
Northern California Cancer Program, Palo Alto, CA, 94304
Lancet; 2(8250):795-797 1981

The epidemiology of advanced breast cancer, characterization and evaluation of patients with advanced disease, types of systemic treatment, prediction of response, and management of locally advanced breast cancer are discussed. Chemotherapy is the preferred initial treatment for patients with pulmonary or liver metastases. For patients without aggressive visceral spread, the choice is between hormone therapy and chemotherapy and is determined by estrogen receptor status. Patients with receptor-positive tumors usually receive endocrine therapy and those with receptor-negative tumors generally receive chemotherapy. Radiotherapy is preferred for locally advanced Stage III tumors. Combined cytotoxic and endocrine treatment is not recommended because of the possible danger of suboptimum use of two potentially effective treatments. Good predictors of response to chemotherapy are not available, but response to endocrine therapy can be predicted by progesterone receptor status. (no Refs)

20. ANDROGEN AND OESTROGEN BINDING IN CYTOSOLS OF HUMAN OVARIAN TUMOURS.

Hamilton TC, Davies P, Griffiths K
Tenovus Inst. Cancer Res., Welsh Natl. School Medicine, The Heath, Cardiff, Wales
J Endocrinol; 90(3):421-431 1981

The specific retention of androgens and estrogens by cytoplasmic components of human ovarian tumors was investigated. High-affinity, low-capacity binding of androgens was observed in 88% of tumor specimens and estrogen binding in 32%. Retention of estrogens did not occur in the absence of androgen binding. The androgen-binding component, of sedimentation coefficient 7.5-8.5S, showed specificity for 5alpha-dihydrotestosterone and 17beta-hydroxy-17alpha-methyl-estra-4,9,11-trien-3-one (R1881). In some instances, competition for R1881-binding sites indicated the presence of progesterone receptor-like binding. The data presented suggest strongly the existence of androgen and estrogen receptors in some ovarian tumors and may be relevant to histopathological classification and therapeutic rationales. (Author abstract) (36 Refs)

21. DESENSITIZATION TO GONADOTROPINS IN CULTURED LEYDIG TUMOR CELLS INVOLVES LOSS OF GONADOTROPIN RECEPTORS AND DECREASED CAPACITY FOR STEROIDOGENESIS.

Freeman DA, Ascoli M
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Proc Natl Acad Sci USA; 78(10):6309-6313 1981

The ability of human choriogonadotropin (hCG) to regulate its receptors and target cell responses has been studied in a clonal strain of cultured Leydig tumor cells (MA-10). Exposure of the MA-10 cells to hCG results in decrease in hCG binding activity which is dependent on time and the concentration of hCG. This decrease is due to a change in the number of receptors rather than in the affinity of the receptors, and it is accompanied by a corresponding reduction in the ability of hCG to stimulate steroidogenesis. Exposure of the MA-10 cells to hCG also resulted in a reduction of the steroidogenic responses to cholera toxin and 8-Br-cyclic-AMP. The hCG-induced loss of steroidogenic responses to these stimuli seems to be due to the stimulation of steroidogenesis rather than to the decrease in hCG receptors because it also can be induced when steroidogenesis is stimulated with cholera toxin or 8-Br-AMP under conditions such that the number of hCG receptors is not reduced. (Author abstract) (21 Refs)

22. CURRENT STATUS OF PROGESTIN RECEPTORS IN CANCER (MEETING ABSTRACT).

Wittliff JL
Department of Biochemistry, University of Louisville Health Sciences Center, Louisville, KY
Clin Chem; 27(6):986 1981

Because the native hormone, progesterone, associates and dissociates rapidly from its binding sites in vitro, several synthetic steroids of high specific radioactivity are used as ligands in clinical assays. The most commonly employed is tritium-labeled R5020, a progestomimetic steroid, which has a high affinity for and dissociates slowly from receptors. Although the subunit structures of progestin receptors in chick oviduct are reasonably well understood, those of breast and uterus are emerging. Currently it is accepted that estrogens, via their own receptor mechanism, are involved in the control of progestin receptors in uterus. Although less is known of this regulatory mechanism in mammary tissues, it appears that analyses of progestin receptors in breast carinomas are helpful in the selection of hormonal manipulation. Patients with breast biopsies containing both estrogen and progestin receptors show an increased likelihood of responding to ablative or additive hormone therapy compared to those with only one type of receptor. Several new clinical trials by national cooperative groups are investigating the relationship between tumor receptor status and a patient's response to antihormone therapy and disease-free survival. These studies require quality assurance steroid receptors analyses and the establishment of uniformity of methods and data expression. (no Refs)

23. EFFECTS OF SODIUM MOLYBDATE ON STABLIZATION OF STEROID HORMONE RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Wong WH
CLMG Clinical Laboratory, Los Angeles, CA, 90057
Clin Chem; 27(6):1078 1981

Effects of the addition of sodium molybdate during the determinations of steroid hormone receptors were assessed for various final concentrations of molybdate and at various temperatures. Estrogen, progesterone, androgen and glucocorticoid receptors were determined in human breast cancer cytosols by dextran-coated charcoal method, with and without addition of sodium molybdate. Results indicated that with the presence of at least 20 mmol/L of molybdate, there was reduction in binding loss when incubated at all the temperatures tested. Significant increases in binding capacity were observed for progesterone and glucocorticoid receptors in some cytosols. Somewhat less increases were also observed for estrogen and androgen receptors in many cytosols. The number of receptor-positive specimens was increased while no specimen was observed to revert from positive to negative after addition of molybdate. Multiple determinations on pooled specimens also yielded better reproducibility of results with the presence of molybdate. We conclude that the addition of sodium molybdate does have a definitely positive stabilizing effect during the incubation of cytosol receptors with radio-labelled steroids. The inclusion of molybdate may be the next step towards the formulation of a standard method for the determination of steroid hormone receptors. (no Refs)

24. DUAL COMPONENT ESTRADIOL BINDING IN LEIOMYOMA AND TUMOR BEARING MYOMETRIUM (MEETING ABSTRACT).

Stevens SR, Otubu A, Besch NF, Besch PK
Department of Obstetrics/Gynecology, Baylor College of Medicine, Houston, TX, 77030
Clin Chem; 27(6):1078 1981

Leiomyomas or uterine fibroids are a common estrogen dependent tumor of women. Our purpose was to assay estrogen binding in human leiomyomas and tumor bearing myometrium by Scatchard analysis using a wide concentration range of [3H]-estradiol-17beta in order to demonstrate the presence of two high affinity estrogen binding proteins, and to quantitate and compare the number of binding sites of each component in the two tissues. Leiomyoma and myometrial tissue cytosols were prepared from hysterectomy specimens from premenopausal women. Serum binding proteins were excluded by receptor precipitation at a final concentration of 30% ammonium sulfate. Unbound steroid was removed by dextran coated charcoal treatment. Two high affinity estradiol binding components presumed to be estrogen receptors were clearly present in both leiomyoma and myometrial cytosols. The concentration of binding sites and the equilibrium dissociation constants (Kd's) of each component were determined by the method of Rosenthal. Nearly identical Kd's of 10(-10) and 10(-9) M were determined for the two components in both tissues. In almost every case the concentration of each estrogen binding component in myomatous tissue was greater than the corresponding concentration in myometrial tissue from the same organ. The difference in concentration of lower affinity sites was larger than the difference in concentration of higher affinity sites and suggests that the role of the lower affinity binding protein may be more significant to the etiology of leiomyomas. (no Refs)

25. SIMULTANEOUS DETERMINATION OF ESTROGEN AND PROGESTERONE RECEPTORS USING 125I-ESTRADIOL AND 3H-R5020 (MEETING ABSTRACT).

Thibodeau SN, Freeman L, Jiang NS
Mayo Clinical, Rochester, MN, 55905
Clin Chem; 27(6):1078 1981

We describe a dual-isotope assay for measuring simultaneously the concentration of estrogen and progesterone receptors in tumor cytosols. the concentrations of these receptors are derived from separate Scatchard-plot analyses of a single dextran-coated charcoal (DCC) assay that incorporates both radioiodinated estradiol and tritiated R5020 as the labeled ligands. Competition studies between these radiol abeled ligands and a number of unlabeled steroids (testosterone, estradiol, diethylstilbestrol, cortisol, progesterone, and R5020) revealed that 3HR5020 and 125I-estradiol bound specifically to their respective receptor. In addition, a comparison of several DCC assays, each of which utilized various labeled steroids (3H-estradiol, 125I-estradiol, 3H-R-5020, or both 125I-estradiol and 3H-R5020) showed that (a) 125I-labeled and 3H-labeled estradiol were equally effective in measuring the concentration of the estrogen receptor (linear regression analysis; y equals 0.98x + 8.99; r equals 0.98; n equals 42) and (b) the concentration of the estrogen and of the progesterone receptors derived from the dual-isotope assay was identical to that obtained from the two respective single-label assays. The dual-isotope DCC assay requires both less time and less tissue because (a) both radiolabeled ligands can be included in the same assay mixture and (b) both radioiodine and tritium can be quantitated simultaneously with a liquid scintillation counter. (no Refs)

26. EFFECT OF GLUCOCORTICOIDS ON THE GROWTH OF LYMPHOID CELL LINES (MEETING ABSTRACT).

Mermod JJ, Newby RN, Bourgeois S
Regulatory Biology Laboratory, The Salk Institute, San Diego, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Glucocorticoids induce cytolysis of sensitive T-lymphoid cell lines in culture. The murine thymoma line WEHI-7 (W7) has been extensively used to analyze this effect of glucocorticoid hormones. This response is mediated by the glucocorticoid receptor, but the events following translocation of the receptor-steroid complex to the nucleus, and the mechanism of cell lysis are entirely obscure. One possible indirect mechanism of glucocorticoid-induced cell death is by inhibition of T-cell growth factor (TCGF or IL2) production that would result in suppression of proliferation. This mechanism does not seem to be implied in the cytolysis of W7 cells or of other murine T-cell lines tested, since the addition of TCGF to the cultures does not overcome the response to glucocorticoids. No variant having a normal receptor but blocked in a later step of the response has ever been obtained. It is conceivable that other functions involved in the response are vital to the cell and that defects in these functions are, therefore, lethal. Genetic studies of lymphocytolysis could be extended by obtaining new types of variants that are supersensitive, rather than resistant, to glucocorticoids. Mutations that amplify rather than abolish to the response may not be lethal, and the characterization of supersensitive variants may help identify new functions involved in lymphocytolysis. Variants of W7 that are supersensitive to glucocorticoids have been isolated, and some of their properties will be discussed. (no Refs)

27. DISTRIBUTION OF CYTOPLASMIC AND NUCLEAR ESTROGEN RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Genz T, Eiletz J
Universitats-Frauenklinik Charlottenburg, Berlin, W. Germany
Acta Endocrinol [Suppl]; 96(240):123 1981

In our study estrogen receptor levels were measured in both compartments of breast cancer tissues. Cytoplasmic estrogen and progesterone receptors were determined by the dextran-coated charcoal technique. Measurement of nuclear binding sites was performed by an exchange assay with some modifications according to Bayard et al. For any sample to be classed as positive in terms of estrogen receptors it had to satisfy the following criteria: yield an unambiguous Scatchard line, levels of 20 fmol/mg protein and 25 fmol/mg DNA for cytoplasmic and nuclear binding sites, respectively. Nuclear receptor values ranged from 25-3,000 fmol/mg DNA with a dissociation constant of approx 3 x 10(-9) M to 12 x 10(-10) M. Eighty tissues (59%) with positive cytoplasmic estrogen receptor contained significant levels of nuclear binding sites in 84.3% of the specimens with and in 73.9% of the specimens without additional cytoplasmic progesterone receptors. Estrogen receptor negative tumors had low levels of nuclear binding sites in 17% only. Different results in receptor distribution in both fractions were found in approx 20% of all breast cancer cells. Preliminary clinical results indicate that the additional measurement of nuclear binding sites for estradiol may give more detailed information about hormone dependence. Fourteen women with metastatic disease could be analyzed. Nine of them had an objective remission undergoing hormone therapy. There was a good correlation between positive as well as negative cytoplasmic and nuclear binding sites in responders and non-responders, respectively. (no Refs)

28. GLUCOCORTICOID-STIMULATED INCREASE IN CHEMOTACTIC PEPTIDE RECEPTORS ON DIFFERENTIATING HUMAN MYELOID LEUKEMIA (HL-60) CELLS.

Brandt SJ, Barnes KC, Glass DB, Kinkade JM
(c/o Kinkade) Dept. Biochemistry, Emory Univ. Sch. Medicine, Atlanta, GA, 30322
Cancer Res; 41(12):4947-4951 1981

The effect of dexamethasone on the HL-60 human promyelocytic leukemia cell line was studied using a radioligand-binding assay for a chemotactic peptide receptor that is found on the surface of mature polymorphonuclear leukocytes. When dimethyl sulfoxide (DMSO) is added to cultures, HL-60 cells undergo morphological and functional differentiation over a period of 6 to 7 days. Differentiation is accompanied by increased binding of the synthetic N-formylated chemotactic peptide N-formylmethionylleucyl[3H]phenylalanine. Binding of N-formylmethionylleucyl[3H]phenylalanine to cells induced to differentiate with DMSO was temperature dependent, specific, saturable, of high affinity, reversible, and proportional to cell number. Dexamethasone increased the number of N-formylated chemotactic peptide receptors in cultures of differentiating HL-60 cells without affecting the affinity of the receptor for the tritiated peptide. This steroid response was dose dependent, proportional in magnitude to glucocorticoid activity, and abolished by cycloheximide. Dexamethasone had little effect on N-formylmethionylleucyl[3H]phenylalanine binding unless DMSO was also present in culture or the cells were first induced by DMSO to differentiate. These results suggest that the glucocorticoid stimulated increase in number of N-formylated chemotactic peptide receptors was mediated by the high-affinity glucocorticoid receptor, involved protein synthesis, and was apparently dependent on differentiation. (Author abstract) (33 Refs)

29. EFFECTS OF 17BETA-ESTRADIOL ON PROGESTERONE RECEPTORS AND THE UPTAKE OF THYMIDINE IN HUMAN BREAST CANCER CELL LINE CAMA-1.

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Cancer Res; 41(12):5004-5009 1981

Two sublines, CAMA-1R and CAMA-1N, were derived from the original CAMA-1 cells after continuous passages in our laboratory. 1R cells were supplemented in culture with estradiol and retained the properties of the original cell line, whereas 1N cells, not supplemented with estradiol, had a partial loss of estrogenic responsiveness. The doubling times for 1R and 1N cells were 2 and 2.4, respectively. These two sublines showed different effects on thymidine uptake after estradiol stimulation. Cells of 1R had a 2-fold greater thymidine incorporation than did the control without estradiol. In contrast, no difference of thymidine uptake was demonstrated in cells of 1N in the presence or absence of estradiol. Both cell lines contained cytoplasmic progesterone receptors with a Kd of 0.56 nM and a sedimentation coefficient of 6 to 7S on a 5 to 20% sucrose gradient. The progesterone receptor level in 1N was about 8-fold higher than in 1R cells. Both sublines exhibited a dose-dependent increase in progesterone receptor levels in response to estradiol with the max stimulation (8-fold increase) reached by using 5 nmol of estradiol. The rate of increase for estradiol-induced progesterone receptor appears to be the same for both sublines; a linear increase was demonstrated between Days 3 and 7 following plating. Our results show that estrogen regulation of thymidine uptake and progesterone receptor induction may be mediated through two separate mechanisms. Thus, following a chronically deficient supply of estradiol to 1N cells, there is apparent loss of responsiveness to estradiol-induced thymidine uptake, but the ability of these cells to respond to estradiol induction of progesterone receptor was retained. (Author abstract) (30 Refs)

30. FREQUENCY OF 1,25-DIHYDROXYVITAMIN D3 RECEPTOR IN HUMAN BREAST CANCER.

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Cancer Res; 41(12):5121-5124 1981

Receptors for 1,25-dihydroxyvitamin D3 have been shown to exist in cultured breast cancer cells and in primary breast cancers. It is reported here that 1,25-dihydroxyvitamin D3 receptor (1,25-DR) was present in 80% of 54 unselected breast cancers. The concentration of 1,25-DR in the 43 receptor-positive tumors was 1.9 +-0.4 fmol/mg protein (SE). There was no correlation between 1,25-DR presence or concentration and the age of the patient or the concentration of estrogen, progesterone, androgen, or glucocorticoid receptors. 1-25-DR was also found in two of three renal cortical carcinomas but only in 3 of 14 gastrointestinal tract carcinomas. The relatively low concentration of 1,25-DR in these breast cancers, compared with that found in cultured breast cancer cells, is partially explained by incomplete 'exchange' with occupied receptors. Since the serum vitamin D-binding protein is not precipitated from serum itself or from tissue homogenates using the polyethylene glycol method, artifactual 1,25-DR levels due to the inevitable contamination of tissue specimens with this protein can be excluded. These findings indicate that 1,25-DR is not a nonspecific marker of cancer. The high frequency of 1,25-DR in the breast cancers may be related to the calcium-transporting ability of breast cancer cells which allows them to grow as osteolytic metastases. (Author abstract) (23 Refs)

31. AUTORADIOGRAPHIC DEMONSTRATION OF UPTAKE AND RETENTION OF 3H-ESTRADIOL AFTER IN VITRO INCUBATION.

Buell RH, Tremblay G
Dept. Pathology, McGill Univ., Montreal, Quebec H3A 2B4, Canada
J Histochem Cytochem; 29(11):1316-1321 1981

An in vitro incubation method is described for the demonstration of 3H-estradiol in sections of mouse uterus by thaw-mount autoradiography. The method involves the incubation of tissue sections in 5 nM 3H-estradiol with a subsequent 2 hr chase in medium containing 3.5 g% bovine serum albumin. The distribution of the silver grains observed compares favorably to that seen by others with dry-mount autoradiography after in vivo injection. The labeling is inhibited by excess estradiol or diethylstilbestrol, but not by progesterone or hydrocortisone. Its subcellular distribution appears predominantly nuclear in presumptive target cells. Some regional variability in degree of labeling is present throughout the sections, but is far less marked within a given area. Because the observed labeling has been retained during a 2 hr chase and can be inhibited, it is likely to represent physiologically significant uptake and retention of 3H-estra diol in target cells. Preliminary results with human mammary carcinoma suggest this method may be applicable to the investigation of estrogen target cells in human tissue. (Author abstract) (37 Refs)

32. OESTROGEN-RECEPTOR STATUS AND SITES OF METASTASIS IN BREAST CANCER.

Campbell FC, Blamey RW, Elston CW, Nicholson RI, Griffiths K, Haybittle JL
Dept. Surgery, City Hosp., Nottingham NG5 1PD, England
Br J Cancer; 44(3):456-459 1981

The estrogen receptor (RE) status of the primary tumor has been assessed in 466 of a consecutive series of 550 patients with primary operable breast cancer. All patients were followed up (without treatment) until the development of recurrence or metastases. Distant metastases have so far occurred in 124 patients and 82 have had symptomatic local or regional recurrence. A significant correlation exists between the RE status of the primary tumor and subsequent patterns of metastasis. Symptomatic metastases to regional lymph nodes are more common with RE- cancers. There is no significant difference in either time of onset or total incidence of distant metastases between patients with RE+ and RE- tumors. Distribution of distant metastases is influenced by RE status: RE+ tumors tend to recur in bone, RE- tumors show affinity for viscera. (Author abstract) (16 Refs)

33. CYTOPLASMIC PROGESTERONE AND ESTRADIOL RECEPTORS IN NORMAL, HYPERPLASTIC, AND CARCINOMATOUS ENDOMETRIA: THERAPEUTIC IMPLICATIONS.

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Am J Obstet Gynecol; 141(5):539-546 1981

This study was designed to determine whether the presence of progesterone receptors (PR) and/or estradiol receptors (ER) could be used to predict progestin responsiveness of recurrent or advanced endometrial cancers. We have demonstrated the presence of physicochemically similar cytoplasmic progesterone and estradiol receptors in normal, hyperplastic, and carcinomatous endometria. All normal endometria contained both PR and ER. Seventy-three percent of endometrial hyperplasias were PR(+) and 93% were ER(+). A decreasing concentration of progesterone receptor activity was observed with increasing tumor anaplasia [Grade 1, 84% PR(+); Grade 2, 55% PR(+); Grade 3, 22% PR(+)] and in irradiated tumors. A statistically significant (p less than 0.001) relationship has been demonstrated between the presence of specific cytoplasmic PR and response to progestin therapy in recurrent or advanced endometrial adenocarcinomas. Thus, we conclude that a PR assay may be used to help select the most appropriate therapy for patients with recurrent or advanced endometrial adenocarcinoma. (Author abstract) (42 Refs)

34. OESTROGEN RECEPTORS AND SURVIVAL IN EARLY BREAST CANCER.

Croton R, Cooke T, Holt S, George WD, Nicolson R, Griffiths K
Dept. Surgery, Royal Liverpool Hosp., Liverpool L69 3BX, England
Br Med J; 283(6302):1289-1291 1981

Estrogen receptor status was related to survival in 414 patients with primary breast cancer. Women with estrogen receptors in their tumors survived significantly longer than those without receptors; this was true for both premenopausal and postmenopausal women and also when the patients were subdivided into those with and without axillary metastases. Patients with axillary metastases and no estrogen receptors in their tumors had the worst prognosis, while women with axillary metastases and estrogen receptors had a death rate similar to that of women with no axillary metastases and no receptors. Patients without estrogen receptors and with no axillary metastases were identified as a high-risk group, and it would seem appropriate to include such patients in future trials of adjuvant therapy in early breast cancer. (Author abstract) (7 Refs)

35. STEROID HORMONE RECEPTORS IN HUMAN MALIGNANT MELANOMA (MEETING ABSTRACT).

Bojar H, Stuhldreier B, Becher H, Goerz G, Merk H, Koldovsky U, Staib W
Physiology Chemistry II, Universitat Dusseldorf, Dusseldorf, W. Germany
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

In an attempt to elucidate the endocrine background of human malignant melanoma (MM) cytosols prepared from biopsies and MM cells in culture have been investigated for the presence of steroid hormone receptors. MM tissue was obtained from 21 patients. Specific estrogen-binding components were present in 9/21 biopsies. In the cytosol of 6 MM's specific 8S estrogen binders were detected. Specific progestin (promegestone)-binding components were demonstrated in 17/20 biopsies. In 7/20 biopsies 8S binding was detected. Specific androgen (methyltrienolone)-binding entities were present in 4/12 tumors. Glucocorticoid receptor activity was present in 12/12 MM's. Ligand specificity experiments indicated a requirement of active glucocorticoids. Human MM cells in culture were found to contain glucocorticoid receptors only. In comparison to endocrine dependent breast cancer, the estrogen and progestin binding capacities of MM are low. The trace concentrations of androgen binders seem to be of no biological significance. In contrast, glucocorticoid receptor concentration in MM is similar to that in human liver, glucocorticoid target organ par excellence. (no Refs)

36. A FLUORESCENT METHOD OF MEASURING ESTROGEN RECEPTORS IN CYTOLOGIC MATERIAL (MEETING ABSTRACT).

Curtin CT, Pertschuk LP, Mitchell V
Moses Taylor Hospital, Scranton, PA
Acta Cytol (Baltimore); 25(4):450 1981

Biochemical methods of measuring estrogen receptors require 1 g of tissue and th us are not satisfactory for cytologic material. We report a histochemical test for measuring estrogen receptors at the cellular level. Fine needle aspirations were performed on 19 ptients with primary or metastatic mammary carcinoma. Representative aspirates were smeared on slides, and the diagnosis was confirmed. Parallel slides were transported on dry ice. Each smear was overlaid with 50 pmol of fluorescienated estradiol-bovine serum albumin ligand conjugate at room temperature for two hr. Parallel slides were exposed to a 100-fold M excess of antiestrogen C1-628. Smears were studied by incident UV light, and percentages of cells exhibiting nuclear, nucleolar and/or cytoplasmic binding were ascertained and graded for intensity of staining from 0 to +++. Successful competition was determined by the presence of significantly less fluorescence in smears exposed to C1-628. Sixteen of 19 patients had biochemical determinations for comparison. Seven patients were receptor positive; six were negative using both determinations. Three cases were weakly positive biochemically and negative by histochemistry. In one of the discrepant cases, the biochemical test was performed two yr previously. In the other two cases, cellular primary tumors may have falsely elevated the biochemical test. (no Refs)

37. OESTROGEN AND ANDROGEN RECEPTORS IN BENIGN PROSTATIC HYPERPLASIA AND CARCINOMA OF THE PROSTATE (MEETING ABSTRACT).

Tilley WD, Keightley DD, Marshall VR
Flinders Medical Centre, Bedford Park, South Australia
Br J Urol; 53(1):74 1981

The measurement of hormone receptors in human breast cancer has now been clearly established as an important predictor of the likely response of these tumors to hormonal manipulation. In attempting to extend this approach to prostatic cancer, cytoplasmic estrogen, progesterone and androgen receptors were measured in 133 men undergoing transurethral resection of the prostate. The incidence of these receptors for estrogen, progesterone and androgen was 16, 33 and 28% respectively. We also found that there was a significant increase in the incidence of both estrogen and progesterone receptors with the age of the patient. This correlation may be of significance in relation to the known increase in the incidence of malignancy with age. The incidence of androgen receptors in the cytoplasm was lower than we would have anticipated in view of the fact that the prostate is an androgen target organ. To examine the possibility that some of the receptors in the cytoplasm were being masked by endogenous androgen or, alternatively, are localized in the nucleus, an exchange assay, as well as a nuclear androgen receptor assay, was developed; using these techniques, the incidence of androgen receptors in the cytoplasm increased from 28 to 58% and all of the nuclear extracts examined were receptor positive. Thus it would appear that receptor patterns are more complicated in benign prostatic tissue than in breast tissue, and that simple cytoplasmic assays may not be sufficient to allow receptor incidence to be used clinically. (no Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

38. LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN ORAL CONTRACEPTIVE-TREATED FEMALE RATS.

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Biochem Med; 26(2):222-230 1981

Treatment of adult female rats with 1/10th tablet of combination-type oral contraceptive (OC), Ovulen-50 (ethynodiol diacetate, 1.0 mg; ethynyl estradiol, 50 ug) for 24 days resulted in a significant increase in lipid content and a small increase in DNA content (per unit body wt) of the liver. Liver regeneration following partial hepatectomy as judged by increase in liver wt and protein, DNA, and RNA contents was significantly lower in the OC-treated animals compared to the controls. Prior to hepatectomy, thymidine incorporation into DNA was significantly higher in the livers of OC-treated rats. This trend reversed after hepatectomy. Histological examination revealed a higher incidence of binucleate cells and mitotic figures in the livers of OC-treated rats prior to hepatectomy but not during regeneration. (Author abstract) (24 Refs)

39. GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY IN HUMAN BREAST CANCER: LACK OF ASSOCIATION WITH OESTROGEN RECEPTOR CONTENT.

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Acta Pathol Microbiol Scand [A]; 89(4):263-270 1981

The correlation between glucose-6-phosphate dehydrogenase activity and different tumor characteristics was investigated in human breast cancer tissue. The enzyme activity was measured by a histochemical method and the estrogen receptor content by a dextran-coated charcoal assay. The proliferative activity of the tumors correlated positively with the glucose-6-phosphate dehydrogenase activity. No correlation was found between enzyme activity and tumor type and menopausal status, age, TNM-class nor estrogen receptor content. Based on this investigation it is concluded that the activity of glucose-6-phosphate dehydrogenase reflects the proliferative status of the tumor but not the hormone dependency of the tumor. (Author abstract) (24 Refs)

40. TAMOXIFEN-INDUCED GENERALIZED LIPIDOSIS IN RATS SUBCHRONICALLY TREATED WITH HIGH DOSES.

Lullmann H, Lullmann-Rauch R
Dept. Pharmacology, Univ. Kiel, Kiel, W. Germany
Toxicol Appl Pharmacol; 61(1):138-146 1981

To determine whether the antiestrogenic and antineoplastic agent tamoxifen (TMX) induces generalized lipidosis, female Wistar rats were kept on a TMX-containing diet for 6-14 wk. The daily TMX doses ranged 100 to 130 mg/kg. Light and electron microscopic examination of liver, popliteal lymph nodes, adrenal glands, anterior pituitary gland, retina, nucleus supraopticus of the hypothalamus, and superior cervical ganglion showed increased numbers of intensely staining lamellated and crystalline-like cytoplasmic inclusions. Necrosis and gradual replacement by abnormal vacuolated cells were observed in the adrenal cortex. The degree of lipidosis depended upon the dose of TMX and duration of treatment. (15 Refs)

41. MODIFICATION OF BENZO(A)PYRENE-INDUCED CELLULAR TRANSFORMATION OF C3H/10T1/2 CELLS BY DEXAMETHASONE AND PREGNENOLONE-16ALPHA-CARBONITRILE (MEETING ABSTRACT).

Kuszynski G, Langenbach R
Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE, 68105
In Vitro; 17(3):223 1981

Most chemical carcinogens exist in the environment in an unreactive form and require metabolic activation to exert their biological activity. Manipulation of the microsomal enzymes has been proposed as a mechanism for controlling carcinogenesis. In this study two compounds, dexamethasone (DEX) and pregnenolone-16alpha-carbonitrile (PCN), are potent inducers of microsomal enzymes in vivo. Since these enzymes are responsible for the metabolism of carcinogens, the effects of these compounds were studied to determine whether increased enzyme activity was correlated with cellular transformation. Both DEX and PCN were found to induce AHH activity in the C3H/10T1/2 cells by about 2 fold and both compounds increased the rate of metabolism of benzo(a)pyrene to water-soluble products. The steroids however had opposite effects on transformation. DEX inhibited cellular transformation by about 65% at 23 uM concentration. PCN, however, was found to increase the frequency of transformation by more than 100%. Therefore, enhanced AHH activity and metabolism does not necessarily lead to enhanced transformation since other pathways of metabolism, carcinogen detoxification, or repair processes may be involved. (no Refs)

42. STIMULATION OF GLUCOCORTICOIDS OF THE LEVELS OF TWO UREA-CYCLE ENZYMES IN CULTURED RAT HEPATOMA CELLS (MEETING ABSTRACT).

Haggerty DF, Spector EB, Lynch M, Kern R, Frank LB, Cederbaum SD
Department of Psychiatry, University of California of Los Angeles, 760 Westwood Plaza, Los Angeles, CA, 90024
In Vitro; 17(3):233 1981

With an aim at developing a model system in cell culture for elucidating the molecular mechanisms regulating urea production in the differentiated mammalian liver, we have investigated the effect of glucocorticoids on two urea-cycle enzymes, arginase and argininosuccinate synthetase, in three permanent rat hepatoma lines, H4-II-E-C3 (H4), MH1C1, and HTC. Whereas the last of these was devoid of either enzymatic activity, the H4 and MH1C1 cells both possessed constitutive levels of each enzyme that were elevated markedly after exposure of the intact cells to hydrocortisone (HC). We report here the characterization of this hormonal effect in the H4 line, in which the stimulation of these enzymic activities by HC is both time- and dose-dependent, requires ongoing cellular protein synthesis, exhibits a satisfactory degree of specificity, is mimicked by other optimal-inducer steroids (dexamethasone and corticosterone), and is blocked by an anti-inducer steroid (fluoxymesterone). We thus conclude that the stimulation of the levels of these two urea-cycle enzymes in the H4 line occurs through a classical glucocorticoidal mechanism and that these liver-derived cells constitute a useful model system for studying the molecular basis for the regulation of the expression of the genes for these two differentiated functions in the mature mammalian liver. (no Refs)

43. THE ROLE OF RECEPTORS IN HORMONE MEDIATED REGULATION OF ALKALINE PHOSPHATASE IN CULTURED HUMAN CANCER CELLS (HELA) (MEETING ABSTRACT).

Antonopoulos PA, Singer RM
Department of Anatomy, Fairleigh Dickinson University School of Dentistry, Hackensack, NJ
Anat Rec; 199(3):12A 1981

HeLa cells have been cloned into two sublines monophenotypic for alkaline phosphatase. HeLa TCRC-1 cell line produced a placental alkaline phosphatase while the HeLA TCRC-2 cell alkaline phosphatase was most similar to the bone/liver type. Our studes on regulation of enzyme activity have indicated that glucocorticoid hormones (Prednisolone) enhanced the activity of alkaline phosphastase in the Regan producing HeLa TCRC-1 cell line while the non-Regan producing HeLa TCRC-2 cell line was unaffected in this respect. This difference of gene expression of the carcinoplacental isoenzyme of the HeLa sublines provides a model with which to further study hormonal regulation of gene expression. We shall report our data on the HeLa cell sublines, TCRC-1 and TCRC-2 with respect to the number of hormonal receptor sites for prednisolone in both the cytoplasmic and nuclear fractions. The mechanism of hormone action on the levels of enzyme activity can be at the gene level directly, or a receptor mediated phenomenon. To this end, we have assayed for the levels of hormone receptors in these two HeLa sublines using a tritium ligand binding method. This method relies on the detection of bound tritium labelled steroid. Free unbound steroid is absorbed using a dextran coated charcoal. (no Refs)

44. COMPARATIVE EFFECTS OF RADIATION ALONE OR ESTROGEN TREATMENTS ON THE FINE-STRUCTURE OF PROSTATIC ACINAR AND STROMAL CELLS IN HUMAN PROSTATIC ADENOCARCINOMA (MEETING ABSTRACT).

Sinha AA, Smith AD, Lange PH, Blackard CE
Department of Genetics and Cell Biology and Urologic Surgery, University of Minnesota, Minneapolis, MN
Anat Rec; 199(3):237A 1981

Effects of radiation alone or estrogen treatments on the fine structure of prostatic acinar, invasive and stromal cells were compared to determine morphological characteristics of residual or surviving cells in the prostatic biopsies of prostate cancer patients during the first two yr of treatments. In the prostate glands, the acini contained light and dark basal cells, columnar/cuboidal cells and degenerating acinar cells. The stroma possessed variable amounts of invasive cells, fibroblasts, smooth muscle fibers, collagen fibers and blood vessels. Morphological analysis of the above cell types indicated that nearly all the prostatic cells were affected similarly by radiation treatment unlike the estrogen treated biopsies in which most of the columnar cells usually involuted into cuboidal cells. Relative to other cell types, the dark cells were more abundant indicating selection of unresponsive cells in estrogen treated patients. The invasive cells were fewer in radiation treated patients than in estrogen treated ones. Our result has shown that in localized tumors of stage III or lower, having moderate to well differentiated tumors, more acinar, invasive and stromal cells were destroyed during the first seven mo of radiation treatment than in estrogen treated patients. In radiation treated patients, most of the residual cells (some of which were neoplastic) were viable based on ultrastructural characteristics and/or on ability to proliferate in short-term tissue culture. In estrogen treated patients, more viable and neoplastic cells were readily observed. (no Refs)

45. ROLE OF ESTROGENS AND GROWTH FACTORS IN PITUITARY TUMOR CELL GROWTH (MEETING ABSTRACT).

Moo JB, Sirbasku DA
Department of Biochemistry and Molecular Biology, The University of Texas Medical School, Houston, TX
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Preliminary evidence suggests that estrogens causes an increase in total protein per cell as measured by flow cytometry methods. Taken together, the data suggest that while estrogens may have an effect on cell metabolism, they do not control complete traverse of the growth cycle. Conversely, estrogen-inducible growth factors derived from rat uteri and kidneys and from rabbit uteri promote continuous growth of GH3/C14 cells in serum-free medium. These observations support our previous proposal that both the uterine and kidney derived activities could act in vivo as sources of protein mediators (estromedins) for estrogen-responsive pituitary cell growth. Efforts to utilize the large scale rabbit uteri and kidney sources for purification are in progress. In other studies we have found no evidence of autocrine/paracri ne production of pituitary cell growth factors by normal pituitary gland or GH3/C14 pituitary tumors. Finally, since a considerable amount of neuroendocrine data exists showing the hypothalamus to produce physiology control substances for anterior pituitary, we have prepared extracts of female rat hypothalamus, cerebellum, cerebum and brain stem, and assayed for growth factor activity using the GH3/C14 cells in serum free medium supplemented only with extract proteins. Hypothalamic extract protein, at levels of up to 94 ug/ml, promoted growth of GH3/C14 cells as measured by an increase in cell number, while extracts of other areas of the rat brain showed no activity. (no Refs)

46. OPPOSITE EFFECTS OF ESTROGENS AND ANTIESTROGENS ON PG SYNTHETASE FROM HUMAN BREAST CANCER (MEETING ABSTRACT).

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Laboratoire de Cancerologie Experimentale, Faculte Nord de, Medecine de Marseille 13326 Marseille Cedex 3, France
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

In-vitro direct effects of estrogen (Es: natural +synthetic) and antiestrogens (Tamoxifen Tam and its derivatives and metabolites) on prostaglandin (PG) synthetase activity in human breast cancer were investigated in an 'overall' microsome preparation obtained from 261 surgical samples of breast cancer for a total wt of 418 g. The enzymatic characteristics of such a representative pool of PG synthetase were found to be Km: 4.76x10-5M and Vmax: 3.6x10(-9) moles/mg protein. The natural Es hormones were all found capable of stimulating PG synthetase activity in a dose-dependent manner. The stimulating potency of Es was decreasing from E2, E3 to E4. E1 and ethynylestradiol have poor effect. E2 maximal effect was reached for 10-5M while E2 10-8M was uneffective. Contrasting the exclusive stimulating nature of Es, Tam and its derivatives exhibited either stimulating or inhibitory effects depending upon both the chemical nature and concentration of the antiestrogen. Tam is only an efficient and direct inhibitor of PG synthetase. Chemical alterations of the ethylene binding induces a loss of activity. By contrast, 4-OH-Tam and desmethyl-Tam which natural metabolites of Tam in human were potent agents in either stimulating or inhibiting PG synthesis at low doses or high doses respectively. Therefore, Tam and its metabolites could behave differently depending upon the tissular dose. (no Refs)

47. PRESENCE OF ECTOPIC BETA-ADRENERGIC RECEPTORS ON HUMAN ADRENOCORTICAL CORTISOL-PRODUCING ADENOMAS.

Hirata Y, Uchihashi M, Sueoka S, Matsukura S, Fujita T

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J Clin Endocrinol Metab; 53(5):953-957 1981

A direct binding study of radioligand [3H]dihydroalprenolol (DHA), a potent beta -adrenergic antagonist, was performed on the particulate fractions of four adrenocortical adenomas (3 cortisol-producing adenomas and 1 aldosterone-producing adenoma) and normal adrenal tissues. The effect of epinephrine on cortisol production was also evaluated in vitro from the cultured tumor cells from one cortisol-producing adenoma. Saturable binding of [3H]DHA to the tumor membranes was observed in two of three cortisol-producing adenomas, but not in the aldosterone-producing adenoma or in normal adrenal tissues. Scatchard analysis of equilibrium binding of [3H]DHA revealed a single class of binding sites on the tumor membranes; the apparent dissociation constant (Kd) was 1 nM in each, and the numbers of binding sites were 108 and 45 fmol/mg protein, respectively. Competition by adrenergic agents with [3H]DHA for binding sites on the membranes from one cortisol-producing adenoma revealed that (+-)propranolol, a beta-adrenergic antagonist, was about 350-fold more potent than phentolamine, an alpha-adrenergic antagonist, suggesting the beta-adrenergic nature of receptor sites. In addition, stereospecificity was demonstrated by about 1,000-fold greater affinity of (-)alprenolol than to (+)alprenolol, both of which are stereoisomers of the beta-adrenergic antagonist. Furthermore, production of cortisol from the cultured tumor cells prepared from the same adenoma was significantly stimulated by epinephrine in addition to ACTH. These data indicate that ectopic beta-adrenergic receptor sites are present in some human adrenocortical tumors which may be functionally related to the activation of adenylate cyclase by catecholamines other than ACTH in those tumors, as previously demonstrated. The mechanism by which such altered cellular membrane characteristics occur in association with neoplastic alteration of the endocrine tissues remains unanswered. (Author abstract) (20 Refs)

48. SCANNING ELECTRON MICROSCOPY OF THE ENDOMETRIAL CELL SURFACE IN POSTMENOPAUSAL WOMEN RECEIVING OESTROGEN THERAPY.

Thom MH, Davies KJ, Senkus RJ, Allen JM, Studd JW
King's Coll. Hosp., London, England
Br J Obstet Gynaecol; 88(9):904-913 1981

The surface ultrastructure of normal and abnormal endometrial cells from patients receiving estrogen therapy for the climacteric syndrome was studied by scanning electron microscopy. Patients with endometrial pathology were treated with oral progestogens. Excessive estrogen stimulation caused proliferation of cilia and microvilli. Cystic hyperplasia was characterized by a proliferation of cilia until they covered more than one-third of the surface area of the endometrium; further proliferation occurred in cases of adenomatous hyperplasia when the surface was almost completely covered with cilia. Cell morphology remained apparently normal until atypical hyperplasia, when occasional cells appeared large and irregular, or adenocarcinoma occurred, when the surface cells appeared large, pleomorphic and sometimes wrinkled, being mostly devoid of cilia. Although cystic hyperplasia was converted to a normal histologic picture of atrophic or pseudo-decidual endometrium by course of progestogen, the deciliated endometrial cells showed persisting abnormal ultrastructural characteristics. (Author abstract) (13 Refs)

49. ANTAGONISM OF DRUGS USED IN LEUKAEMIA THERAPY TO THE KILLING OF HUMAN LYMPHOBLASTOID CELLS BY STEROID.

Gledhill RM, Norman MR
Dept. Chemical Pathology, King's Coll. Hosp. Medical Sch., Denmark Hill, London SE5 8RX, England
Br J Cancer; 44(3):467-471 1981

The interactions of prednisolone with drugs currently used in the chemotherapy of acute lymphoblastic leukemia were studied in human lymphoblastoid cell line CCRF-CEM-7, the cells of which are lysed by pharmacological concentrations of glucocorticoids. Determination of cell survival in the presence of prednisolone alone and in combination with 6-mercaptopurine (MP), methotrexate (MTX), cytosine arabinoside (Ara-C), and daunomycin (DMN) showed no consistent interaction between MTX and prednisolone. Interactions between DMN and prednisolone varied between mild synergism and antagonism, while both MP and Ara-C showed consistent antagonism. (14 Refs)

50. A CYPROHEPTADINE-REVERSIBLE DEFECT IN ACTH CONTROL PERSISTING AFTER REMOVAL OF THE PITUITARY TUMOR IN CUSHING'S DISEASE.

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Box 111, MCV Station, Richmond, VA, 23298
N Engl J Med; 305(21):1244-1248 1981

Two phases of cortisol feedback suppression of ACTH were studied in nine patients who had adrenalectomy for Cushing's disease and in five hypoadrenal patients (controls). Among the nine patients, four had been treated by adrenalectomy alone and presumably had ACTH-secreting pituitary tumors, and the five others were studied greater than 2 yr after transsphenoidal removal of an ACTH-secreting microadenoma. Cortisol (CTS; 100 mg, iv, in 120 min) was infused 24 hr after the last po dose of cortisone. After the first cortisol infusion, cyproheptadine (CYH; 24 mg/day, po for 7 days) was given. CTS infusion was repeated 2 hr after the last dose of CYH and 24 hr after the last dose of cortisone. After 30 min of CTS infusion, plasma ACTH fell 28.0 +-10.1% (P less than 0.01) in the hypoadrenal control patients, but only 2.7 +-2.6% (P less than 0.01) in the nine patients treated by adrenalectomy. In the nine patients, the fall in ACTH after 30 min of CTS infusion was significantly greater after CYH (24.4 +-4.8%, P less than 0.005) than before. This enhanced negative feedback was similar in both groups of patients. After CYH was given, CTS levels during the second infusion were similar in patients and controls. The results suggest that higher centers may have a role in the pathophysiology of Cushing's disease. (29 Refs)

51. MODULATION BY RETINOIC ACID AND CORTICOSTEROIDS OF COLLAGENASE PRODUCTION BY RABBIT SYNOVIAL FIBROBLASTS TREATED WITH PHORBOL MYRISTATE ACETATE OR POLY(ETHYLENE GLYCOL).

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Biochim Biophys Acta; 677(3/4):424-432 1981

Monolayer cultures of rabbit synovial fibroblasts can be stimulated experimentally to produce large quantities of latent collagenase by treatment with phorbol myristate acetate (PMA) or by formation of multinucleated giant cells with poly(ethylene glycol). We studied the ability of all-trans-retinoic acid and/or corticosteroids to modulate collagenase production induced experimentally. Concomitant addition of PMA along with retinoic acid (10(-6) M) inhibited production of collagenase by 60-100%. 10(-7) M retinoic acid was partially effective, reducing collagenase by 20%. Addition of dexamethasone (10(-7) M) to cultures gave results similar to retinoic acid at 10(-6) M. Inhibition of collagenase synthesis was confirmed by SDS-polyacrylamide gel electrophoresis of medium from cultures treated with PMA, or with PMA and retinoic acid or dexamethasone. Addition of both retinoic acid and prednisolone to cultures reduced collagenase production more effectively than either drug alone; both drugs at 10(-10) M for 2 days lowered collagenase levels to 50% of control, while each drug alone at 10(-10) M had no effect. Addition of retinoic acid (10(-6) M) to cultures containing multinucleated giant cells lowered collagenase production by 70-85%. Removal of the drug resulted in full recovery. Our data indicate that all-trans-retinoic acid inhibited collagenase production induced by PMA or poly(ethylene glycol) and that this inhibition was additive with corticosteroids. (Author abstract) (51 Refs)

52. A CLINICOPATHOLOGIC CORRELATION OF THE IDIOPATHIC HYPEREOSINOPHILIC SYNDROME. II. CLINICAL MANIFESTATIONS.

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(c/o Fauci), NIH, Building 10, Room 11B13, Bethesda, MD, 20205
Blood; 58(5):1021-1026 1981

The idiopathic hypereosinophilic syndrome, a disorder characterized by peripheral blood and bone marrow eosinophilia associated with single or multiple organ system dysfunction attributable to tissue invasion by eosinophils has, in the past, been associated with an extremely poor prognosis. Recently, we reported the favorable impact of a therapeutic protocol consisting of prednisone and/or hydroxyurea on the morbidity and mortality of this syndrome. We have reviewed the clinical and hematologic features upon admission and the subsequent clinical courses of 32 patients with this disease referred to the NIH between 1965 and 1979 in an effort to determine which features suggest a more rapidly progressive course. A grading system based on 22 clinical features involving the eight organ systems commonly affected by the illness was devised. The disease followed a more aggressive course in patients with evidence of cardiac or neurologic dysfunction at the time of initial NIH evaluation. Although splenomegaly, in and of itself, caused little morbidity, splenic enlargement at presentation appeared to be a predictor of a more aggressive course. The clinical grading system accurately predicted which patients would require no specific antihypereosinophilic therapy, which patients would respond adequately to corticosteroids, and which patients would require therapy with cytotoxic agents. It is proposed that this clinical grading system, and the hematologic grading system outlined in the accompanying report be used as aids in the selection of initial therapy in this group of patients. (Author abstract) (12 Refs)

53. GLUCOCORTICOIDS REGULATE EXPRESSION OF DIHYDROFOLATE REDUCTASE CDNA IN MOUSE MAMMARY TUMOUR VIRUS CHIMAERIC PLASMIDS.

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Nature; 294(5838):228-232 1981

Fusions between the mouse mammary tumor virus long terminal repeat and a mouse dihydrofolate reductase cDNA have been constructed in a SV40 vector. When these plasmids are transferred into recipient cells, the production of dihydrofolate reductase is regulated by glucocorticoid hormones. These results define a hormonally responsive region of the viral genome. (Author abstract) (26 Refs)

54. DEMONSTRATION OF PREGNANCY-ASSOCIATED ALPHA2-GLYCOPROTEIN (ALPHA2-PAG) IN PREGNANT, ESTROGEN-TREATED AND BREAST CANCER-BEARING RATS.

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Oncodev Biol Med; 2(5):345-354 1981

A high mol wt (382,000 daltons) pregnancy-associated alpha alpha2-glycoprotein (A-PAG) was detected in the sera of pregnant, estrogen-treated, and breast cancer-bearing female Sprague Dawley rats. Double immunodiffusion patterns gave immunologic reactions of identity. A-PAG was not detected in the serum of either normal or injured adult female or male rats. The relative concentrations of A-PAG measured in pregnant rats by rocket immunoelectrophoresis increased rapidly and progressively, and reached a max during the third trimester of gestation then decreased to undetectable levels within 3 days postpartum. The serum concentrations of A-PAG in estrogen-treated female rats also reached a max level equal to that found in pregnant rats. The evidence presented here indicates that this high mol wt pregnancy-associated alpha2-glycoprotein is analogous to its human counterpart, and that this animal model system is suitable to study sites of synthesis, and the biologic function of this protein. (36 Refs)

55. DEXAMETHASONE INHIBITS A HEME-INDEPENDENT EVENT NECESSARY FOR TERMINAL DIFFERENTIATION OF MURINE ERYTHROLEUKEMIA CELLS.

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Biochem Biophys Res Commun; 102(4):1342-1349 1981

The effect of exogeneous hemin on the inhibition, by dexamethasone (DEX), of hexamethylene bisacetamide (HMBA)-induced differentiation of murine erythroleukemia cells was investigated. When 100 uM hemin was added to cells cultured for 44 hr in the presence of 4 milliM HMBA and 100 nanoM DEX, there was an increase in the proportion of benzidine-positive cells, which was due to the appearance of Hb in the cytoplasm of these cells. Cells cultured in the presence of HMBA were shown to have a low plating efficiency due to their commitment to terminal differentiation. However, although the addition of hemin to the culture with HMBA and DEX caused the proportion of benzidine-positive cells to rise to more than 80%, the plating efficiency was not reduced. This indicate that the addition of hemin did not override the inhibition by DEX of commitment to terminal differentiation whereas the inhibition of the appearance of Hb was suppressed. The induction of the nuclear protein IP25, which is associated with reprogramming to limited growth ability in several other systems, was not inhibited by DEX. These experiments show that DEX inhibits at least one heme-independent step necessary for commitment to terminal differentiation but not for globin gene expression. (25 Refs)

56. GUINEA-PIG AFP DURING NORMAL ONTOGENESIS, LIVER CARCINOGENESIS, AND UNDER HORMONE TREATMENTS (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:P6 1981

Guinea-pig alpha fetoprotein (AFP) was purified to homogeneity, characterized, and a radioimmunoassay was developed. Serum AFP level in fetal guinea-pig remains in the mg/ml range up to the 8th gestational wk and then drops rapidly. The electrophoretic and lectin affinity molecular variants of AFP change during ontogenesis, probably in relation with changes in carbohydrate composition of the protein. The liver and the yolk sac are the main sites of AFP synthesis during fetal life with the stomach and the small intestine contributing smaller amounts, as measured by peptide pulse labeling assays in vivo. Compared to other species, serum AFP levels are very high in normal adult guinea-pig; these levels are reduced dramatically by administration of glucocorticoids or ACTH. The hormone effect is rapidly reverse d upon withdrawal. In guinea-pigs fed with diethylnitrosamine, serum AFP increases at the time liver tumors appear; there is no early induction and the increase is much less than in rats under similar treatment. (no Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

57. THERAPEUTIC STRATEGIES IN THE TREATMENT OF BREAST CANCER: ADJUVANT POSTOPERATIVE THERAPY AND CYTOSTATIC TREATMENT IN METASTATIC STAGE.

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Wien Klin Wochenschr; 93(17):531-541 1981

Breast cancer (BC) accounts for 14% of all malignant tumors. BC includes infiltrating duct carcinoma and medullary carcinoma. Four stages of disease are recognized according to the TNM classification system. Prognosis depends on tumor stage, location of metastases, the length of apparent disease-free state before diagnosis of metastases, and the response to treatment. Tumors bearing specific estrogen receptors respond better to treatment than tumors without these receptors. Postoperative adjuvant chemotherapy increases survival rates, but late side effects require further study. Cytostatic therapy (CT) may be used in inoperable cases. Cytostatic monotherapy for metastatic BC has been replaced by combinations of cytostatic drugs. CT following local treatment of solitary metastases increases chances of long-term remission. Postmenopausal cases may be treated with antiestrogens. A combination of CT and hormone therapy may be used after ovariectomy in premenopausal cases. Selection of treatment modality depends on the number of metastases, their location, the length of disease free interval, and the risk of complications. (37 Refs) (In GER)

58. EXOGENOUS ESTROGENS AND ENDOMETRIAL CANCER: A CASE-CONTROL STUDY AND ASSESSMENT OF POTENTIAL BIASES.

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Am J Epidemiol; 114(4):497-506 1981

Eighty-eight cases with newly diagnosed carcinoma of the endometrium and 177 age-matched neighborhood controls were interviewed to test the hypothesis that exogenous estrogens lead to an increased risk of endometrial cancer. Forty-five percent of the cases and 22% of the controls reported a history of estrogen use which yielded an odds ratio of 2.9 (confidence interval (CI) 1.7-5.1). Women with 5 or more yr of estrogen use had an odds ratio of 8.6 (CI 3.2-23.0). Approx 80% of the estrogen users had used conjugated equine estrogens. For these women the odds ratio was 4.0 (CI 1.9-8.4) for daily dosages of more than 1 mg of estrogen. Several sources of bias which might affect the estrogen association were investigated. These included comparability of cases and controls, selection procedures, difference between estrogen users and nonusers, exclusion of controls who had hysterectomy, source of estrogen information, and differential recall. The concept of medical surveillance was evaluated by access to medical care and prior history of dilatation and curettage. The strong association between exogenous estrogen use and endometrial cancer remained after consideration for the effects of these biases. (Author abstract) (23 Refs)

59. SCREENING OF ASYMPTOMATIC WOMEN FOR ENDOMETRIAL CANCER.

Koss LG, Screiber K, Oberlander SG, Moukhtar M, Levine HS, Moussouris HF
Dept. Pathology, Albert Einstein Coll. Medicine, Montefiore Hosp. Medical Center, Bronx, NY
CA; 31(5):300-317 1981

This report describes the preliminary results of a feasibility study of detection of endometrial carcinoma in an asymptomatic population of women aged 45 and above. The initial sample of 1,280 women was evaluated by several cytologic smear techniques and by two endometrial sampling methods assigned by computer. The clinical approaches and the techniques used are detailed. During this initial period of study, eight histologically proved endometrial cancers were diagnosed, two of which were deeply invasive. With one exception, the eight patients were either obese or had a history of treatment with conjugated estrogens. A relatively small number of women with endometrial hyperplasia of various types were also identified. The accuracy of the detection methods and their long-term impact on morbidity and mortality cannot be assessed as yet. Incidentally, a small number of cancers and precancerous states of organs other than the endometrium have also been diagnosed. (Author abstract) (31 Refs)

60. TOPICAL ASPECTS OF HORMONE THERAPY FOR PROSTATE CARCINOMA.

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Helv Chir Acta; 48(3/4):391-395 1981

Four endocrine treatment modalities for prostate carcinoma were analyzed in a Phase III study including randomization and classification by prognostic parameters: 1. Primary orchiectomy with hormones only after tumor progression; 2. Primary estrogens with orchiectomy only after tumor progression; 3. Primary treatment with cyproterone acetate (CA) or medroxyprogesterone acetate; 4. Combined hormone therapy [estramustine phosphate (EP), cyproterone acetate, or estrogens plus bromocriptine]. CA was no more or less cancerostatic than estrogen, but its side effects were fewer. Estrogens and CA caused a rise in serum prolactin that justified use of the antiprolactin agent bromocriptine. Simultaneous orchiectomy provided no advantage, except in cases of urine retention. Late orchiectomy could be used if other measures failed to stop tumor progression. EP was recommended only in cases of relapse. (14 Refs) (In GER)

61. THE ROLE OF ESTROGEN IN HEPATIC NEOPLASIA: AN EXPERIMENTAL MODEL (MEETING ABSTRACT).

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Toronto Western Hospital, Toronto, Ontario, Canada
Gastroenterology; 80(5,part2):1354 1981

The administration of estrogens to humans has been associated with the development of benign and malignant hepatocellular neoplasms. We present here a rat model which demonstrates that stilbestrol (DES) promotes the development of hepatic noeplasms in rats previously initiated with diethylnitrosamine (DEN). Thirty-two male rats (Fisher 344) were given a single dose of DEN (200 mg/kg, ip) followed 4 wk later by DES (5 mg, po) twice weekly for up to 50 wk. Other rats given vehicle only served as controls. DES was stopped at the time of sacrifice or 11-29 wk prior to sacrifice. All rats given both DEN and DES developed grossly visible hepatic hyperplastic nodules, measuring up to 29 mm in diameter, after 20 wk of DES. Rats given DEN alone or DES alone did not develop nodules. Microscopic hyperplastic foci also developed in rats given DEN plus DES or DES or DEN alone. The foci developing in rats given DES were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinylestradiol (0.2 mg twice weekly) in male rats and of DES in female rats was observed. The data indicate that estrogens promote neoplasia, perhaps by increasing hepatocytic mitotic activity thereby allowing previously initiated cells to evolve into neoplastic clones. Although comparison with human disease should be made with caution, the parallels to human oral contraceptive-associated hepatic adenomas and carcinomas is obvious. It is possible that some women have latent 'initiated' cells that are unusually responsive to estrogen. (no Refs)

62. GROWTH INHIBITION BY DEXAMETHASONE IN CLONAL VARIANTS OF HAMSTER MELANOMA CELLS: CHARACTERIZATION OF BIOLOGICAL RESPONSE AND ROLE OF MEDIUM COMPONENTS (MEETING ABSTRACT).

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Molecular Biology Division, University of Southern California, Los Angeles, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Dexamethasone (10 nM) inhibits the growth, alters the morphology and decreases the final cell density in RPMI 3460 Syrian hamster melanoma cells. We have isolated clonal variants of RPMI 3460, one of which (clone 6) exhibits the same three biological responses to dexamethasone (DM) the parental cell line. The other clone (clone 5), while exhibiting the decrease in final cell density, fails to exhibit the growth inhibition and morphological alterations. Since progesterone antagonizes the biological responses of clone 5 and clone 6 cells to DM, it appears that all the responses are mediated by glucocorticoid receptors. Experiments in which DM is added to or removed from logarithmically growing clone 6 cultures indicate that growth inhibition can be induced or reversed in less than 24 hr after DM addition or removal. Moreover, DM which is added during early or mid-logarithmic growth is able to evoke the decrease in final cell density and DM which is removed during early or mid-logarithmic growth has no effect on final cell density in clone 5 and clone 6 cultures. Interactions of DM with factors in fetal calf serum are unnecessary for DM action in logarithmically growing clone 6 cells. Moreover, these factors must not be involved in the different responses of clone 5 and clone 6 cells to DM. Studies with conditioned medium suggest that the different phenotypes of clone 5 compared to clone 6 cells are not due to differences in the ability of the two cell lines to alter the medium by producing extracellular resistance or sensitivity factors, either in the presence or absence of DM. (no Refs)

63. MENINGEAL CARCINOMATOSIS.

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Arch Neurol; 38(11):696-699 1981

Records of 33 meningeal carcinomatosis patients from 1970-79 were reviewed to examine current therapeutic methods. Carcinomas seen included breast, lung, malignant melanoma, pancreas, and liver. Patients' most frequent symptoms were confusion, headache, and difficulty walking. Cranial nerve dysfunction accounted for 79% of these findings. The time between diagnosis of the symptoms varied from 6 wk to 6 yr. Twenty-six had evidence of active systemic disease at the time of neurologic diagnosis. Examination of cerebrospinal fluid (CSF) initially showed 28 abnormalities; neoplastic cells were found in 24 cases. Subsequent CSF exams showed neoplastic cells in all cases with cell counts ranging from 0 to 550/cu mm. The most successful treatment appeared to be intrathecal administration of methotrexate (0.25 mg/kg) combined with radiotherapy. Fourteen showed at least symptomatic improvement. Mean survival for all tumors treated with corticosteroids, with or without radiotherapy was 5.6 mo. Sixty percent of patients with improved clinical signs also showed improvement in CSF findings. Death in most cases resulted from systemic rather than neurologic disease. Meningeal carcinomatosis should be suspected in any cancer patient who shows signs of alteration of consciousness, cranial nerve findings, or development of radicular disease. Recognition of a pattern of clinical disease rather than abnormal CSF is important for diagnosis. New therapeutic approaches are needed due to the lack of effectiveness and potential toxicity of current treatments. (30 Refs)

64. EFFECT OF HIGH LEVEL OF ENDOGENOUS CORTICOSTERONE ON GLUCOCORTICOID RECEPTORS IN THE SPLEEN OF RATS BEARING AH130 TUMORS.

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Gan; 72(5):754-761 1981

Increase in spleen wt and in the number of spleen cells was observed in rat bearing AH130 (solid-type) tumors, which have high plasma corticosterone concentrations. In contrast, decrease in the number of spleen cells was observed in adrenalectomized rats without tumors which were injected every 3 hr with a dose of corticosterone sufficient to produce a plasma level close to the physiological range in rats with advanced stage tumors. In the spleen of adrenalectomized, corticosterone-treated rats, the binding capacity and affinity of cytosol receptors for dexamethasone decreased and were low on day 3 after the last injection of corticosterone, when no corticosterone was detectable in the spleen and the receptors in the liver cytosol showed max binding capacity. Neither the level of cytosol receptors in the spleen nor their affinity for dexamethasone, however, were changed in tumor-bearing rats on day 3 after adrenalectomy when the level of cytosol receptors and affinity for steroid of the thymus were still very low. The activity of alanine aminotransferase increased appreciably in the spleen cytosol of glucocorticoid-treated rats, but not in tumor-bearing rats, which have high plasma corticosterone levels. These data show that administration of corticosterone at physiological concentrations affected the spleen cells, the glucocorticoid receptors and alanine aminotransferase, but that in AH130 tumor-bearing rats, which have a high level of endogenous corticosterone, the spleen enlarged without change in the above parameters. Thus, spleen cells from rats with tumors were more resistant to glucocorticoid than those from animals without tumors. However, there seemed to be no correlation between the level of glucocorticoid receptors and glucocorticoid resistance. (Author abstract) (38 Refs)

65. LONG-TERM CULTURE OF NORMAL AND LEUKEMIA HUMAN BONE MARROW.

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Haematol Blood Transfus; 26:276-288 1981

A method for the long-term culture of human marrow cell populations based on modifications of the murine system is presented. Normal marrow specimens from ribs of patients undergoing thoracotomy, aspirates of normal sternal marrow from patients undergoing cardiovascular surgery, and aspirates from the iliac crests of patients with acute myeloid leukemia (AML) before treatment, while in remission, and during relapse were cultured in Fisher's and McCoy's medium. Adipocyte-containing confluent stromal layers could be initiated and maintained for periods of at least 5 mo in either medium when supplemented with both horse serum (HoS) and hydrocortisone. Granulocyte-macrophage progenitor cells (CFUc) were supported for up to 12 wk in Fisher's growth medium supplemented with hydrocortisone and 25% HoS or 12.5% HoS and 12.5% fetal bovine serum (FBS), but the number of colony-forming cells recovered was usually less than 50 per 10(5) cells assayed. In contrast, McCoy's medium supplemented with both FBS and HoS contributed to significantly greater yields of CFUc. The results suggest that hematopoiesis in long-term liquid cultures of human marrow is dependent upon the presence of lipid-laden adipocytes. (27 Refs)

66. CORTICOSTEROID DEPENDENCE OF CONTINUOUS HEMOPOIESIS IN VITRO WITH MURINE OR HUMAN BONE MARROW.

Greenberg HM, Parker LM, Newburger PE, Said J, Cohen GI, Greenberger JS
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Haematol Blood Transfus; 26:289-293 1981

A system for continuous in vitro hemopoiesis using human marrow is reported. Human marrow was obtained from biopsies of femur or rib. Cultures were grown under varying conditions. Production of granulocyte-macrophage progenitor cells (GM-CFUc) required freshly added hydrocortisone, as in murine marrow cultures. Further requirements, not necessary for murine marrow cultures, included delayed removal of RBC and pH 7.0-7.5 with PCO2 at 3-5%. Adherent cell populations showed more fibroblastic proliferation than murine cultures. Within fibroblasts and macrophages in the stroma were 'cobblestone' areas of tightly packed cells. Continuous human marrow cultures produced granulocytes with normal morphology which produced esterase and myeloperoxidase. Over 80% of cultures tested contained granulocytes and macrophages. Granulocytes showed normal ingestion, respiratory burst activity, degranulation, and bacterial killing. GM-CFUc were produced for more than 20 wk by the method. (16 Refs)

67. STUDIES OF THE ENDOCRINE, PARACRINE AND AUTOCRINE CONTROL OF MAMMARY TUMOR CELL GROWTH (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Classical endocrine studies have shown that both estrogens and prolactin are required for growth of several types of carcinogen induced mammary tumors of experimental animals. However, despite the best efforts by many laboratories, the dramatic trophic effects of these hormones seen in vivo have been elusive in vitro. Our data, obtained with the MTW9/PL rat mammary tumor cell line, as well as data obtained by others with the MCF-7 and T47-D human mammary tumor lines, have shown that estrogens are required for optimum tumor formation by these cells in vivo, but either no or minimal mitogenic effects of estrogens are demonstrable in culture. To reconcile this observation, we have asked whether estrogen-regulated growth factors may be involved in mammary tumor growth in vivo. We have considered three possible mechanisms by which this process may occur: endocrine control; paracrine control; and autocrine control. We conclude from our studies that all three mechanisms may function in vivo, and that in addition, the differences between estrogen-responsive mammary tumor growth in vivo and autonomous growth in vivo may be related to the ability of the autonomous cells to produce paracrine/autocrine type growth factor constitutively. (no Refs)

68. THE MULTIPLE ROLES OF ESTROGEN IN ESTROGEN-DEPENDENT RENAL CLEAR-CELL CARCINOMA OF SYRIAN HAMSTER (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Estrogen (estradiol [E2] or diethylstilbestrol [DES]), when implanted subcutaneously into male Syrian hamster, elicits renal clear-cell carcinoma after approx 6-8 mo. Estrogen alone causes this effect, ie no cocarcinogen is required for tumor initiation or growth response. Studies conducted in our laboratories and elsewhere indicate that the elevated level of estrogen in the hamster results in a variety of different responses and biochemical effects which in a concerted fashion lead to the phenomenon called renal clear-cell carcinoma. Tumor initiation by Estrogen: DES and E2 induce peroxidase activity and microsomal P450 enzymes in a variety of tissues. In turn, peroxidase and microsomal P450 enzymes oxidize DES to a quinoid structure. DES quinone, a chemically unstable and reactive substance, may spontaneously rearrange to beta-dienestrol or, in the vicinity of cellular macromolecules, may covalently bind to DNA. DES-DNA adduct formation was studied in vitro under various conditions. Estrogen Dependence of Tumor Growth: H301 tumor cells, which are derived from the estrogen-dependent renal clear-cell carcinoma of Syrian hamster, remain estrogen dependent in culture or in host animals. Upon removal of the hormone implant, tumors immediately shrink in size and disappear within 10 days. Estrogen concentration in tumor tissue is low (12-30% of estrogen uptake of liver), despite the presence of estrogen receptors in tumor tissue. (no Refs)

69. EFFECT OF ESTROGEN ON CELL PROLIFERATION, ULTRASTRUCTURE, AND SECRETORY PROTEINS IN HUMAN BREAST CANCER CELL LINES (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

It is debated whether estrogens directly stimulate the growth of breast cancer. We have therefore looked to the effects of estrogens on two human breast cancer cell lines MCF7 and T47D established from pleural metastasis. The cells were cultured in medium containing 10 to 1% fetal calf serum (FSC) decreased in steroid after charcoal (DCC) treatment. Cell proliferation was evaluated by DNA assay (GABA) and protein synthesis by incorporation of 35S-methionine followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and fluorography. Estrogens at physiological concentrations: a) stimulated the growth of the two cell lines; b) altered the ultrastructure of the cells by increasing microvilli and blebs at the cell surface and by transforming 40% of them into secretory cells with secretory granules and Golgi saccules; c) stimulated the synthesis of glycoproteins which were released into the culture medium. One major protein was 46,000 daltons and 53,000 daltons mol wt for the MCF7 and the T47D respectively. Preliminary characterization of these proteins will be reported. The antiestrogens, tamoxifen and 4-hydroxytamoxifen, inhibited these three series of effect and displayed no stimulatory activity on these three parameters. Other steroid hormones were inactive as long as they did not activate the estrogen receptor. We conclude that estrogens are able to stimulate the growth of breast cancer cells in culture as previously reported by M Lippman. The mechanism of their effect either direct or permissive on factors present in the serum or indirect via the estrogen induced proteins secreted in the medium will be discussed. (no Refs)

70. CHARACTERIZATION OF A NEW HORMONALLY RESPONSIVE HUMAN BREAST CARCINOMA CELL LINE (MEETING ABSTRACT).

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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

A breast carcinoma cell line has been established from a bony metastasis taken from the femur of a 56 yr old woman. The cells grow in culture as an adherent monolayer which is organized in distinct acinar clusters. They have a doubling x of 60 hr in RPMI 1640 supplemented with 15% fetal bovine serum. No cell growth is observed if cells are cultured in medium to which steroid free fetal calf serum has been added and prolonged exposure to steroid free serum results in cell death. Cell viability can be pres erved if steroid free serum is supplemented with insulin. The cells release large quantities (60 urokinase units/10(7) cells/24 hr) of a 70,000 mol wt plasminogen activator that is immunochemically distinct from urokinase. The plasminogen activator secreted by these cells can be inhibited by an antibody prepared against the enzyme secreted by melanoma cells cultured in vitro. These breast carcinoma cells also contain the mammary specific enzyme, lactose synthetase. Growth in vitro and 3H-thymidine incorporation into DNA were stimulated by insulin (0.1 ug/ml). Plasminogen activator synthesis was enhanced by insulin (0.1 ug/ml) and estrogen (10-10M) and inhibited by testosterone (10-10M). The availability of a new cell line with phenotypic markers and patterns of hormonal responsiveness characteristic of breast epithelium is of importance for the study of the cell biology of mammary neoplasia and our results emphasize the potential value of plasminogen activator synthesis as a measure of susceptibility to hormonal effects. (no Refs)

71. METABOLIC ACTIVATION OF DIETHYLSTILBESTROL BY PROSTGLANDIN SYNTHETASE AS A MECHANISM FOR ITS CARCINOGENICITY (MEETING ABSTRACT).

Bennett S, Marshall W, O'Brien PJ
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The synthetic estrogen diethylstilbestrol (DES) induces kidney tumors in hamsters and genital tract tumors in rodents. Cervicovaginal alterations including carcinoma were also observed in the female offspring of DES treated women, as were certain teratogenic changes in the genital tract of their male progeny as a result of its transplacental toxicity. Metzler et al 1978 have suggested that peroxidases of estrogen target organs are responsible by catalyzing DES oxidation to intermediate that bind to nucleic acids and other cellular macromolecules. Our research shows that prostaglandin synthetase could also be a catalyst. Seminal vesicular microsomes and uterine microsomes readily catalyzed the binding of C14 diethylstilbestrol to DNA and protein in the presence of arachidonate but not NADPH. Similar results were obtained with C14 estradiol and could explain the association of estrogens and cancer of tissues whose growth is effected by estrogen. DES also induces liver necrosis in vivo. Blackburn et al 1977 have shown that liver microsomes with NADPH catalyzes the binding of DES to DNA. We have also found that cumene hydroperoxide is much more effective than NADPH in catalyzing this binding. (no Refs)

72. ADAPTATION VERSUS SELECTION AS THE MECHANISM RESPONSIBLE FOR THE RELAPSE OF PROSTATIC CANCER TO ANDROGEN ABLATION THERAPY AS STUDIED IN THE DUNNING R-3327-H ADENOCARCINOMA.

Isaacs JT, Coffey DS
James Buchanan Brady Urological Inst. Johns Hopkins Hosp., 600 North Wolfe St., Baltimore, MD, 21205
Cancer Res; 41(12):5070-5075 1981

The Dunning R-3327-H rat prostatic adenocarcinoma is a well-differentiated, slow-growing, serially transplantable tumor of spontaneous origin. When intact male rats bearing such an exponentially growing H-tumor sc are castrated, tumor growth abruptly stops, demonstrating the initial androgen sensitivity of this tumor. Eventually, however, after an extended period, the tumor invariably relapses and once again appears to grow exponentially. At the time of relapse, the tumor is no longer androgen sensitive but has irreversibly progressed to a completely insensitive state. The mechanism responsible for this irreversible progression has been demonstrated by fluctuation analysis not to be due to environmentally induced adaptation of initially androgen-dependent H-tumor cells to a new androgen-independent state. Instead, the progression is due to the basic heterogeneity of the original H-tumor (ie, it is composed of a mixture of preexisting clones of both androgen-dependent and androgen-independent tumor cells). Following castration, only the preexisting clones of androgen-independent tumor cells are able to continue exponential growth; the androgen-dependent tumor cells stop proliferating and die. Thus, androgen ablation creates a host environment in which the androgen-independent tumor cells have a highly selective growth advantage over the androgen-dependent cells. Eventually, with time, this selective growth advantage results in a tumor which is completely composed of androgen-independent cells. It is the continuous proliferative growth of these androgen-independent tumor cells which leads to the relapse phenomenon. (Author abstract) (4 Refs)

73. EFFECT OF ANTINEOPLASTIC AGENTS ON HUMAN BREAST CARCINOMA AND CHORIOEPITHELIOMA TRANSPLANTED INTO ATHYMIC NUDE MICE.

Revazova ES
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (9):79-83 1981

The effect of hormone therapy and chemotherapy on growth of transplanted human breast carcinoma and chorioepithelioma was studied in athymic BALB/c mice. Animals with tumor xenografts received single or repeated (5x) ip injections of dactinomycin (DM), methotrexate (MTX), vincristine, 5-fluorouracil, cyclophosphamide, adriamycin, or lomustine. Hormones (testosterone, cortisone, and hexestrol) were administered sc or po on day 4 after tumor transplantation. Chemotherapy failed to inhibit the growth of human breast carcinoma. Testosterone provided significant inhibition of breast carcinoma growth from day 10 of administration. DM and MTX were effected against xenografter chorioepithelioma; repeated administration provided more effective inhibition of chorioepithelioma growth than single admin istration. (7 Refs) (In RUS)

74. DISSEMINATED BREAST CANCER. EASING LIFE WITH ENDOCRINE THERAPY.

Gordan G, Vaughan C
Univ. California Sch. Medicine, San Francisco, CA
Consultant; 21(11):141-142,147,150-152,157,160-162 1981

A review of likely candidates for endocrine treatment of breast cancer, available forms of therapy, and indications for its use are presented. Tumors rich in estrogen receptors are more likely to respond to endocrine therapy than tumors that are poor in estrogen receptors. Critical levels of estrogen receptor protein are 700 femtomoles/g in postmenopausal women and 300 femtomoles/g in premenopausal women. Probability of achieving regression increases with age and jumps dramatically at menopause. Less vital sites of metastasis such as skin and lymph nodes carry the best prognosis; visceral metastases such as lung, liver, or brain have the poorest response rate. Probability of achieving regression with endocrine therapy decreases greatly if cytotoxic agents have been administered. Available forms of endocrine therapy include ablative procedures (oophorectomy, adrenalectomy, hypophysectomy) and additive hormone therapy (antiestrogens, androgens, estrogens). Clinical approaches include assessing a patient's status through physical and x-ray examination and bone and liver scans. Therapy should progress from the least to the most toxic option. Premenopausal women with widespread metastatic diseases usually respond to oophorectomy; postmenopausal women usually respond to additive hormone therapy (antiestrogens). Treatment should be changed only if there is evidence of tumor progression. Endocrine therapy often prolongs and greatly improves quality of life. Endocrine-induced regressions of metastatic breast cancer usually last longer than those resulting from cytotoxic chemotherapy. (6 Refs)

75. ADVANCED OVARIAN CARCINOMA: RESPONSE TO ANTIESTROGEN THERAPY.

Myers AM, Moore GE, Major FJ
Div. Hematology, Dept. Medicine, Denver General Hosp., 750 Cherokee St., Denver, CO, 80204
Cancer; 48(11):2368-2370 1981

Three patients with Stage III serous cystadenocarcinoma of the ovary were successfully treated with estrogen antagonist therapy after failure of cytotoxic chemotherapy. All had histologic confirmation of progressive or persistent disease. High titers of estrogen receptor protein (ERP) and progesterone receptor protein (PRP) were detected in one patient prior to tamoxifen therapy. One patient had a complete remission lasting for 18 mo. The other patients had partial responses and were able to return to normal activities. Simultaneous or prior sequential cytotoxic chemotherapy did not negate the effectiveness of the estrogen antagonists. (Author abstract) (6 Refs)

76. ANDROGEN-INDUCED REMISSIONS AFTER ANTIESTROGEN AND HYPOPHYSECTOMY IN STAGE IV BR EAST CANCER.

Manni A, Arafah BM, Pearson OH
Univ. Hosp. Cleveland, 2074 Abington Rd., Cleveland, OH, 44106
Cancer; 48(11):2507-2509 1981

Fluoxymesterone (Halotestin), 10 mg po BID, was given to 33 women with Stage IV breast cancer who had previously been treated with the antiestrogen tamoxifen (Nolvadex) and of whom 17 had also undergone hypophysectomy. Objective remissions were obtained in 13 patients (39%) with an av duration of 11+ mo. Response rate to fluoxymesterone was similar in patients who had previously responsed to tamoxifen and in those who had failed Duration of response was longer in the former group (12+ vs 8 mo), but this difference was not statistically significant. Of 17 patients who had been previously treated with tamoxifen and hypophysectomy, 7 obtained further remission from fluoxymesterone for an av duration of 10 mo. Two patients with remissions from fluoxymesterone had previously failed to respond both to antiestrogen therapy and to the removal of the pituitary gland. Androgens appear to be an effective sequential endocrine treatment of Stage IV breast cancer after tamoxifen and hypophysectomy. The mechanism by which androgens induce tumor regression in some patients is probably not an antiestrogenic effect or an indirect effect mediated through the pituitary gland, but perhaps a direct action at the tumor level. (Author abstract) (11 Refs)

77. A COMPARISON OF ESTROGEN USE BY WOMEN WITH ENDOMETRIAL CANCER, GYNECOLOGIC DISORDERS, AND OTHER ILLNESSES.

Stavraky KM, Collins JA, Donner A, Wells GA
Dept. Epidemiology and Biostatistics, Univ. Western Ontario, London, Ontario N6A 5B7, Canada
Am J Obstet Gynecol; 141(5):547-555 1981

Exogenous estrogen use was determined by interview in 206 endometrial cancer patients, 191 women with nonmalignant gynecologic disorders, and 199 women with other illnesses. Separate comparisons of these patients with gynecologic and other illness control subjects provided estimates of the risk of endometrial cancer among estrogen users, adjusted for the effects of confounding variables, of 1.5 (95% confidence limits 0.9 and 2.7) and 4.8 (2.7 and 8.4), respectively. In both comparisons, risk increased with increasing duration of use; regardless of duration of use, risks were higher among users of estrogen within 12 mo of diagnosis than among past users. The effects of bias, including surveillance bias, on the results were considered and it was concluded that the true risk was not less than the case/gynecologic control estimate and was likely to approach the case/other control estimate. (Author abstract) (17 Refs)

78. GROSS AND HISTOPATHOLOGIC EFFECTS OF MEDROXYPROGESTERONE ACETATE AND PROGESTERONE ON THE MAMMARY GLANDS OF ADULT BEAGLE BITCHES.

Concannon PW, Spraker TR, Casey HW, Hansel W
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Fertil Steril; 36(3):373-387 1981

Medroxyprogesterone acetate (MPA: 0.2-75 mg/kg, im, every 3 mo for 1-1.5 yr) was administered to intact, ovariectomized, or hypophysectomized beagles in groups of 6-12 animals each. Intact, noncycling controls received progesterone implants (3-22 cm/kg). MPA equal or greater than 2.0 mg/kg completely suppressed ovulatory cycles, and the suppression was associated with the maintenance of elevated MPA serum levels. MPA treatment (10 and 75 mg/kg) resulted in an increased incidence of multiple, large mammary gland nodules (5-11 mm). These nodular lesions consisted of simple or complex lobular hyperplasia, simple or complex adenomas, and benign mixed tumors; no malignant tumors were found. The nodules occurred after 4-6 of treatment in older dogs and after 8-15 mo in young dogs. Ovariectomy did not affect tumor induction by 75 mg/kg MPA, but adenoma incidence was significantly lower in hypophysectomized than in intact dogs. Low progesterone doses prevented ovarian cycles and higher doses resulted in some degree of mammary enlargement, glandular activity, and nodular development. (29 Refs)

79. CONSERVATIVE TREATMENT OF UTERINE LEIOMYOMA WITH THE ANTIESTROGEN ANTIPROGESTERONE R-2323.

Coutinho EM
Maternidade Climerio Oliveria, Salvador-Bahia, Brazil
Int J Gynaecol Obstet; 19(5):357-360 1981

Use of R-2323 for the suppression and reduction of uterine myomas in premenopausal women is illustrated by the case of an 18-yr-old nulligravida who had been attempting to become pregnant for 1 yr. Symptoms included prolonged menstrual bleeding and dyspareunia. Initially diagnosed as pregnant, subsequent examination by a gynecologist revealed a uterine myoma with recommendation of a total hysterectomy. Further evaluation revealed a 15 cm subserous myoma with bilateral tube occlusion. The patient was treated with 5 mg R-2323 po qod for 2 mo followed by 5 mg twice weekly for 14 mo. Abnormal bleeding ceased at the end of 2 wk; the patient was amenorrheic during the entire therapy. Periodic ultrasonography revealed gradual atrophy of the tumor to approx one-third its original size. Upon discontinuation of therapy, two periods of menstrual bleeding occurred, ceasing with onset of a twin pregnancy. R-2323, a potent 19-norsteroid used as a contraceptive and treatment for benign breast tumors and endometriosis, can also be used for conservative treatment of uterine leiomyoma. (5 Refs)

80. ANDROGEN STIMULATED CHEMOTHERAPY IN THE DUNNING R-3327 PROSTATIC ADENOCARCINOMA.

Grossman HB, Kleinert EL, Lesser ML, Herr HW, Whitmore WF
Section Urology, Univ. Michigan Medical Center, 1405 East Ann St., Box 03, Ann Arbor, MI, 48109
Urol Res; 9(5):237-240 1981

The effect of testosterone (T: 2 mg, sc) on tumor response to methotrexate (MTX: 0.58 mg/kg, ip, for 5 consecutive days followed by a 16-day rest period) was studied in 20 castrated Copenhagen rats bearing transplanted, hormone-responsive Dunning G strain adenocarcinomas. Tumor growth curves for this group were compared with curves for sham-operated controls and animals treated by castration, castration + MTX, or castration + T. The castrated group treated with T and MTX exhibited the least tumor growth and was the only group differing significantly from the control group; however, no increased survival (median, 33 days) was apparent. (5 Refs)

81. ACTIVITY OF THE ANTIOESTROGEN TRIOXIFENE AGAINST N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMAS.

Rose DP, Fischer AH, Jordan VC
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Eur J Cancer Clin Oncol; 17(8):895-898 1981

The therapeutic efficacy of a new antiestrogen, trioxifene, was compared with that of tamoxifen and ovariectomy against rat mammary tumors induced by N-nitrosomethylurea. In control animals, all but 1/59 tumors either progressed (52) or remained static (6) and 31 new tumors appeared. All three modes of therapy were highly effective. Trioxifene mesylate, (300 ug sc daily) induced regressions in 26/61 (42.6%) tumors, and stasis in 13 (21.3%). Nine new tumors appeared during trioxifene treatment. Tamoxifen (200 ug sc daily), produced regression of 22/50 tumors (44.0%), while 19 (38.0%) remained static and 2 new tumors developed. Ovariectomy caused regression of 35/56 (62.5%) tumors, growth was inhibited in another 8 (14.3%) and 2 new tumors developed. Regression after ovariectomy was greater compared with trioxifene therapy (p less than 0.04), but no different for ovariectomy and tamoxifen, or tamoxifen and trioxifene. The relative binding affinity (RBA, OE2 = 100) of trioxifene (8.8-11) for NMU-induced mammary tumor estrogen receptors was consistently 4-5x greater than that of tamoxifen. The comparative study in vitro did not parallel the finding in vivo. However, the RBA of monohydroxytamoxifen, a metabolite of tamoxifen, was the same or 2x greater than that of estradiol, suggesting that tamoxifen's action may be facilitated by conversion to active metabolites. Further study of trioxifene's metabolites may increase our understanding of its mechanism of action in vivo. (Author abstract) (17 Refs)

82. EFFECTS OF MEGESTROL ACETATE ON GROWTH AND SECRETION OF A PITUITARY TUMOR.

Lamberts SW, Janssens EN, Bons EG, Zuiderwijk JM, Uitterlinden P, De Jong FH
Dept. Medicine III, Erasmus Univ. Rotterdam, Univ. Hosp. Dijkzigt, 40 Dr. Molewaterplein, 3015 GD Rotterdam, The Netherlands
Eur J Cancer Clin Oncol; 17(8):925-931 1981

The effect of the administration of the 6-methylated progestagen megestrol acetate on the growth of the estrogen-induced transplantable PRL/ACTH-secreting rat pituitary tumor 7315a was investigated. A significant inhibition of tumor growth was observed only during the last wk of a 4 wk period of drug administration (6 mg/kg). Administration of megestrol acetate suppressed the total content and the ability to release PRL, ACTH and LH of the pituitary gland of tumor bearing rats. Further, a significant suppression of the anterior pituitary, ovarian and uterine wt was observed in the megestrol acetate treated animals. Megestrol acetate did not exert a direct effect on PRL, ACTH and LH secretion by normal rat pituitary glands incubated in vitro. We conclude that megestrol acetate exerts in the model used a suppressive effect on PRL, ACTH and LH release and led to a diminution of the pituitary content of these hormones, while it has also anti-estrogenic and anti-androgenic properties. The effects of the drug help further explain its beneficial effects in metastatic breast, endometrial, renal and prostatic cancer in man. (Author abstract) (30 Refs)

83. PEROXIDASE ACTIVITY IN MAMMARY TUMORS - EFFECT OF TAMOXIFEN.

Levy J, Liel Y, Feldman B, Aflallo L, Glick SM
Div. Endocrinology, Soroka Medical Center, Ben-Gurion Univ. Negev, Beer-Sheva, Israel
Eur J Cancer Clin Oncol; 17(9):1023-1026 1981

Dimethylbenz(a)anthracene (DMBA)-induced tumors in rats were studied for changes in size, cytosolic estrogen (ER) and progesterone (PgR) receptors, and for peroxidase activity before treatment, after 15 days of treatment with the anti-estrogen tamoxifen, and 15 days following cessation of the treatment. Mean size of the tumors decreased significantly during the treatment period to 1/3 the original size and ER and PgR decreased significantly to 1/5 their original levels. Peroxidase activity increased 30-fold. All the changes reversed significantly 15 days after cessation of tamoxifen treatment. These results are consistent with a previous study in which regression of the tumors was induced by castration and recovery was brought about by treatment with estradiol. In DMBA-induced mammary tumors in rats, peroxidase activity in regressing and growing tumors is in inverse relation to changes in tumor size, ER and PgR, which are accepted indicators of estrogenic activity. (Author abstract) (16 Refs)

84. EFFECTS OF SIX ANTICANCER DRUGS ON PLURIPOTENT STEM CELLS IN MICE TREATED WITH TESTOSTERONE PROPIONATE (MEETING ABSTRACT).

Bogliolo GV, Massa GG, Pannacciulli IM
University of Genoa, Viale Benedetto XV, 16132 Genova, Italy
Exp Hematol; 9(Suppl9):135 1981

Bone marrow pluripotent stem cells were assayed in C57B1/C3H mice as colony forming units (CFUs) by the Till and McCulloch transplant method. The femur content and the proliferating fraction of CFUs were determined at different days after i m injection of 450 mg/kg body wt of testosterone propionate (TP). An initial (day 1) decrease and then a slow, progressive rise of CFUs were observed with a peak at day 5 after TP administration. In order to assess possible TP induced modifications of the suppressive effect of anticancer drugs on pluripotent stem cell population, TP treated mice received a single dose, respectively of azathioprine, hydroxyurea, vinblastine, cyclophosphamide, 1,3-bis(2-chloroethyl)-1-nitrosourea and doxorubicin. The drugs were injected 2 or 4 days after the hormone. The bone marrow CFUs were determined 24 hr after drug administration. The toxic effect of the drug was compared with that observed in controls not treated with TP. The CFUs fraction surviving in the bone marrow after the drug administration was similar to or lower than that found in the controls. Considering that the decrease of bone marrow CFUs following cytotoxic drug administration may be explained either by their death or by removal due to differentiation into committed progenitors, this finding does not exclude a possible protective effect of TP hemopoietic depression induced by anticancer drugs. (no Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

85. IMMUNODEFICIENCY.

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Nippon Rinsho; 39(6):70-80 1981

Causes, types, and patterns of infection associated with primary immunodeficiency syndromes, infection associated with secondary immunodeficiency syndromes, and diagnosis and treatment of immunodeficiency diseases were discussed. Malignant tumors were considered to be one of the causes of secondary immunodeficiency syndromes. Various types of immunostimulators and antitumor agents such as alkylating agents, pyrimidine derivatives, purine derivatives, alkaloids, antineoplastic agents, enzymes, and hormones were discussed with respect to the primary types of malignancies (eg lymphogenous tumors, leukemias, carcinomas, and sarcomas) and their efficiency in treatment. Influence of adrenocortical steroids on immunological function was analyzed with respect to the influence on T-lymphocytes, B-lymphocytes, and phagocytes. Immunological status of patients with recurrent or chronic acute leukemia, early stage or advanced solid tumors, and localized or spreading Hodgkin's disease was analyzed with respect to lymphocyte counts, delayed hypersensitivity reactions, inflammatory response, etc. (14 Refs) (In JPN)

86. CLINICAL AND IMMUNOLOGICAL INVESTIGATION OF PATIENTS WITH PROSTATE TUMORS.

Romics I, Feher J, Horvath J, Kisbenedek L, Balogh F
Urologische Klinik, Medizinische Semmelweiss-Universitat, Ulloi ut 78/b, H-1082 Budapest, Hungary
Z Urol Nephrol; 74(8):567-570 1981

Cellular and humoral immune reactivity were measured in 35 patients with histologically confirmed prostate carcinoma (PC). Av patient age was 67 yr. Measurements were made before transurethral prostate resection, cytostatic, and estrogen treatments. Tumors were classified as Stage A (0 cases), B (4 cases), C (18 cases), or D (13 cases). Stage B tumors were disregarded because of insufficient patients. Of 31 Stage C or D tumors, 2 were carcinoma scirrhosum, 1 was cribriform carcinoma, and 28 were adenocarcinoma. Twenty patients with adenoma of the prostate served as controls. Blastic lymphocyte transformation in the presence of phytohemagglutinin was significantly reduced in PC patients (24 +-12%) compared with controls (62 +-7%). No significant differences in levels of IgG or IgM were noted. Levels of acute phase reactant protein alpha-1-antitrypsin were higher (4.62 g/liter) in PC patients than in controls (2.91 g/liter). Transferrin was reduced in both PC and control patients compared with normal individuals. Results confirm that immune reactivity is disturbed in prostate carcinoma patients. The usefulness of immunotherapy in PC cases is suggested. (15 Refs) (In GER)

GENERAL REVIEWS ON STEROID HORMONES

87. DETERMINANTS OF SUSCEPTIBILITY AND RESISTANCE TO FELINE LEUKEMIA VIRUS INFECTION. I. ROLE OF MACROPHAGES.

Hoover EA, Rojko JL, Wilson PL, Olsen RG
Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Rd., Columbus, OH, 43210
JNCI; 67(4):889-898 1981

The role of autochthonous peritoneal feline macrophages (Mtheta) in the age-related resistance of cats to feline leukemia virus (FeLV) was investigated by a study of the functional properties and FeLV susceptibility of Mtheta from kittens and adult cats and the effect of hydrocortisone (HC) and silica on Mtheta-FeLV interactions. Although the phagocytic functions of isolated Mtheta from kittens and adults were equivalent, the mean FeLV susceptibility of Mtheta from kittens was 5x that of Mtheta from adult cats, thus establishing a direct correlation between the age-related susceptibility of cats and Mtheta from cats to FeLV. Mtheta of viremic cats were found to be infected with FeLV in vivo; virus titers were slightly higher than those obtained after in vitro infection of Mtheta. Mtheta from cats that had experienced regressive FeLV infection were not significantly more resistant to FeLV infection in vitro than were Mtheta from naive adult specific-pathogen-free cats. HC, which has been shown to enhance the in vivo FeLV susceptibility of cats, also enhanced the permissiveness of Mtheta from cats to FeLV in vitro (600-fold for Mtheta from adult cats and 200-fold for Mtheta) from kittens. Mtheta permissiveness to FeLV was highly sensitive to HC and occurred in Mtheta infected in vivo or in vitro. In parallel with the effect of HC on the natural resistance of cats to FeLV, administration of silica before virus inoculation also markedly enhanced the FeLV susceptibility of adult cats. Silica was toxic for isolated Mtheta but not for lymphocytes in vitr o, and silica produced monocytopenia and neutrophilia, delayed skin allograft rejection, and augmented feline oncovirus-associated cell membrane antigen antibody responses in vivo. These experiments indicate that Mtheta were linked to the natural resistance of cats to FeLV and that the temporary elimination of Mtheta functions (eg, by silica) and/or the conversion of the Mtheta-FeLV relationship from a nonpermissive to a permissive state (eg, by corticosteroids) resulted in failure of early virus containment, in persistent virus amplification in hemolymphatic tissues, and in subsequent FeLV-related proliferative or antiproliferative disease. (Author abstract) (72 Refs)

88. DETERMINANTS OF SUSCEPTIBILITY AND RESISTANCE TO FELINE LEUKEMIA VIRUS INFECTION. II. SUSCEPTIBILITY OF FELINE LYMPHOCYTES TO PRODUCTIVE FELINE LEUKEMIA VIRUS INFECTION.

Rojko JL, Hoover EA, Finn BL, Olsen RG
Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Road, Columbus, OH, 43210
JNCI; 67(4):899-910 1981

The interplay between feline leukemia virus (FeLV) and feline lymphocytes (lc) infected in vitro or in vivo was investigated. Surface marker analysis and viral infectivity (VI) assays of lc populations were used to determine susceptibility of lc subsets to FeLV. The principal FeLV-replicating cell in the mesenteric lymph node of persistently infected, preleukemic cats was a nonadherent, complement receptor (CR)-bearing lc (B-cell). The lymph nodes of preleukemic cats also had increased numbers of uninfected T-cells [cells forming rosettes with guinea pig RBC (GPE)] and cells with receptors for the Fc portion of 7S IgG (FcgammaR cells) as compared with lymph nodes of age-matched specific-pathogen-free (SPF) cats. The induction of productive infection of feline peripheral blood mononuclear WBC (PBL) in vitro depended on a 48-hr in vitro preincubation period before virus exposure. The equivalent susceptibility of whole and adherent cell-depleted PBL to productive infection and the failure of hydrocortisone to enhance viral infection were compatible with identification of the FeLV-replicating cell as an lc. Furthermore, lc from susceptible SPF kittens replicated 50x as much FeLV as did lc from resistant adult SPF cats. The lc productively infected with FeLV after in vitro exposure were more precisely identified with the use of Ficoll-Isopaque density gradient separation of rosetted and non-rosetted lc. Whole PBL, GPE rosette-positive PBL (T-cells), and CR-positive PBL (B-cells) were permissive to FeLV infection, and max VI was evident at 14 days after exposure. The substantial (1,325-fold) increment in VI found in the FcgammaR-depleted PBL suggested a role for FcgammaR cells in the containment of FeLV infection. Unstimulated mononuclear WBC from blood, spleen, lymph node, thymus, and marrow were susceptible to productive FeLV infection after in vitro exposure. Th e degree of spontaneous DNA synthesis in marrow, thymus, and spleen but not lymph node or PBL was inversely related to permissiveness to viral replication. Mitogen activation of lc was associated with decreased viral replication when either T-cell mitogens (concanavalin A, phytohemagglutinin, or pokeweed mitogen) or a B-cell mitogen (dextran sulfate) was used. Virus production by spleen cells and PBL was enhanced twofold to 10-fold by prior lc stimulation by the B-cell mitogen, lipopolysaccharide, or protein A-bearing Staphylococcus aureus, a mitogen for feline T-cells with FcgammaR. Both productively infected (preincubated) and nonproductively infected (freshly isolated) PBL transferred infectious FeLV to autochthonous peritoneal macrophages (Mtheta); most of the virus in PBL-peritoneal Mtheta cocultures was produced by adherent cells, irrespective of whether the adherent or nonadherent cell population was inoculated originally. (Author abstract) (49 Refs)

89. MODERN APPROACHES TO THE TREATMENT OF BREAST CANCER.

Joss R, Leuenberger U, Zava D, Goldhirsch A, Brunner KW
Institut fur Medizinische Onkologie, Inselspital Bern, 3010 Bern, Switzerland
Praxis; 70(38):1638-1646 1981

Recent achievements in breast cancer therapy are reviewed. The determination of estrogen receptors is of prognostic significance; receptor positive tumors are less likely to recur than negative ones, and the median survival of patients with negative primary tumors is significantly shorter than that of patients with positive tumors. Estrogen receptors are of very great significance for the elimination of patients who would not benefit from hormone therapy. The selection of the patients can be improved by the additional determination of progesterone receptors. Primary surgery, which should be mainly modified radial mastectomy, is indicated in Stages T1-3a, followed by adjuvant chemotherapy in women with axillary lymph node involvement and in premenopausal women. Hormone therapy, chemotherapy, and possibly surgery are indicated in Stages T3b-4b. (42 Refs) (In GER)

90. STEROID HORMONE RECEPTORS AND THEIR RELEVANCE FOR THE THERAPY OF MAMMARY CANCERS.

Heise E
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Arch Geschwulstforsch; 51(8):727-736 1981

The hormone sensitivity of human breast cancer can be determined by analysis of cytoplasmic estradiol receptors. Many (60%) receptor-positive breast tumors respond to hormone therapy, while receptor-negative tumors do not. In the latter tumors, hormone receptor interaction may be impaired. The simultaneous determination of estradiol and progesterone receptor status increases the correlation between receptor status and hormone sensitivity to 80%. A high degree of conformity has been found among primary and metastatic tumors and recurrences. (35 Refs) (In GER)

91. CONJUGATED ESTROGENS AND BREAST CANCER RISK IN WOMEN.

Hoover R, Glass A, Finkle WD, Azevedo D, Milne K
Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(4):815-820 1981

The relationship between conjugated estrogen(s) (CE) and breast cancer was investigated by the examination of the records of 345 women with newly diagnosed breast cancer and 611 healthy controls belonging to a prepaid health plan. Use of CE was associated with a 40% elevation in risk [relative risk (RR) = 1.4; 95% confidence interval = 1.0-2.0]. The RR was 1.3 for menopausal women with intact ovaries and 1.5 for those with ovaries removed. There was statistically significant evidence of a dose-response relationship with the three measures of dose evaluated. RR's rose to about twofold for women with 10 or more CE prescriptions noted in their charts, for those with 5 yr or more between their first and past prescription, and for those with a usual daily dose of 1.25 mg or more. The RR associated with having ever used CE and with long-term use was highest among those women with a family history of breast cancer. These data support the hypothesis that long-term use of CE is associated with increased breast cancer risk. (Author abstract) (41 Refs)

92. ADVANCES IN THE TREATMENT OF BREAST CANCER.

Helman P
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S Afr Cancer Bull; 25(1/2):19-23 1981

A report of seven areas of advances in the understanding and treatment of breast cancer is presented. The radiation dosage for mammography has been reduced to under 5% of 1 rad to the midbreast region with an increase in the quality of the picture. This dose is considered minute in view of mammography's great potential benefits. More nonpalpable, minimal of occult breast cancers are being discovered due to modern screening techniques. Treatment by mastectomy appears superior to local excision. A third advance is the ability to predict hormone or cytostatic therapy. About 70% of patients have estrogen receptors (ER) in the tumor. High ER values respond well to hormone therapy, while low ER values do not. However ER estimating requires sophisticated techniques and personnel. Radical mastectomy is being questioned as a routine therapeutic method. Other researchers claim similar survival rates with little or no surgery combined with radiotherapy. However there are no results superior to those obtained with modified radical mastectomy. Chemotherapy appears more effective for post menopausal women than premenopausal women with heavy axillary invasion. Higher doses appear to insure higher response rates. In view of its toxicity, chemotherapy is indicated only when prognosis would be significantly increased. Breast reconstruction is actively practiced and usually gives excellent results. Hormone therapy for advanced disease shows promise if only for its lack of complications. Combination of hormone and chemotherapy is believed to give superior response rates (73%) as compared to 52% when given singly. A cure for cancer is still unknown but these advances result in a lessening of the burden of cancer. (14 Refs)

93. UTERINE LEIOMYOMATA: ETIOLOGY, SYMPTOMATOLOGY, AND MANAGEMENT.

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Dept. Obstetrics and Gynecology, Baylor Coll. Medicine, Houston, TX, 77030

Fertil Steril; 36(4):433-445 1981

To improve understanding of the etiology and symptomatology of uterine leiomyomata, a review of literature is presented along with assessment of 4,714 myomectomies and records of 59 personal cases. Etiological consideration include histogenesis, estrogen, growth hormone, and progesterone. Symptomatology includes menorrhagia, infertility, pelvic pain and pressure, polycythemia, ascites, impingement, and related complications. The technique of myomectomy is dealt with in detail. A plan for management of uterine leiomyomata is presented for asymptomatic and symptomatic patients, both those desirous of fertility and those not desirous of fertility. (71 Refs)

94. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

Epidemiologic data, methodological problems associated with study of epidemiologic characteristics, and causal factors for pituitary adenomas are reviewed. Clinical features and treatment of pituitary adenomas are summarized. Incidence and prevalence are presented with respect to age, pituitary tumors in children and adolescents, time trends, sex differences, geographic variations, and multiple endocrine adenomatosis syndrome Type I. Exogenous risk factors presented are radiation, chemical carcinogens, estrogens, and oral contraceptives. Included are analyses of pituitary tumors as a proportion of all CNS neoplasms from selected studies, male:female ratios of incidence rates of pituitary tumors from selected reports, pituitary adenomas as a proportion of all primary CNS neoplasms from selected countries, av annual incidence rates/100,000 population for pituitary adenomas from selected countries, effects of diet, I131, and x-rays on induction of pituitary tumors in mice, incidence rate of pituitary tumors in female mice following total body neutron- and x-radiation, and frequency of pituitary adenomas in women with postpill vs non-postpill amenorrhea or amenorrhea-galactorrhea from selected reports. (154 Refs)

OTHER RELATED STUDIES

95. HYPERSECRETION OF AN ABNORMAL FORM OF FOLLICLE-STIMULATING HORMONE ASSOCIATED WITH SUPPRESSED LUTEINIZING HORMONE SECRETION IN A WOMAN WITH A PITUITARY ADENOMA.

Wide L, Lundberg PO

Dept. Clinical Chemistry, Univ. Hosp., S-750 14 Uppsala, Sweden

J Clin Endocrinol Metab; 53(5):923-930 1981

Pituitary tumors producing FSH have hitherto been reported only in males, all of whom have had normal or raised LH levels in serum. This report describes a female with a pituitary adenoma associated with supranormal serum levels of FSH. The FSH was also qualitatively abnormal when compared with FSH in the serum of other postmenopausal women, had a lower apparent mol wt on gel chromatography, and was less negatively charged, as shown by electrophoresis. The results of LRH tests and suppression tests with ethinyl estradiol indicated autonomy of the FSH-producing adenoma. The FSH level increased concomitant with tumor enlargement and decreased after surgical removal of the pituitary adenoma or pituitary irradiation. The serum level of the glycoprotein alpha-subunit was raised about 100-fold. Any free FSH beta-subunits were not detectable in serum. The abnormal FSH had antigenic sites in common with both the alpha- and beta-subunits of FSH. The LH level was extremely low, and there was no response to LRH tests or ethinyl estradiol treatment. After gel chromatography, a small amount of LH, corresponding to 1/50th of the av for the patient's age, was detected at the position for normal LH. There was no GH response to insulin-induced hypoglycemia, while the cortisol increase was normal. Thyroid and adrenal functions were normal. The PRL level was within the normal range and increased slightly after estrogen treatment. (Author abstract) (25 Refs)

96. PELIOSIS HEPATIS ASSOCIATED WITH CAVERNOUS HEMANGIOMA AND HEPATOCARCINOMA.

Herrera LO, Glassman CI, Teixido RA, Oglesby JT, Lopez Andrade E, Rodrigue RB

Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263

Am Surg; 47(11):502-506 1981

Peliosis hepatis is a rare lesion characterized by blood-filled cavities randomly distributed in the liver. It has been associated with the administration of medications such as androgen-anabolic steroids, estrogens, oral contraceptives, and azathioprine. Its diagnosis is most reliably obtained by arteriogram and liver biopsy. Treatment consists of the discontinuance of those medications known to induce liver changes. Surgical treatment is reserved for those cases where a concomitant neoplasm or aneurysm is found. (Author abstract) (10 Refs)

97. A SCREENING TEST TO IDENTIFY ALDOSTERONE-PRODUCING ADENOMA BY MEASURING PLASMA RENIN ACTIVITY: RESULTS IN HYPERTENSIVE PATIENTS.

Hiramatsu K, Yamada T, Yukimura Y, Komiya I, Ichikawa K, Ishihara M, Nagata H, Izumiyama T
(c/o Yamada) Dept. Medicine, Inst. Adaptation Medicine, Sch. Medicine, Shinshu Univ., Matsumoto, Japan
Arch Intern Med; 141(12):1589-1593 1981

In an attempt to devise a screening test for aldosterone-producing adenoma (APA) among hypertensive patients, the serum sodium and potassium levels, plasma renin activity (PRA), plasma aldosterone concentration, and aldosterone-PRA ratio were measured in 348 patients with hypertension. Nine patients with a substantially elevated aldosterone-PRA ratio were selected and hospitalized for further investigations. All nine patients were then recognized by scintigraphy with labeled cholesterol, venography, and surgical excision as having APA. The serum concentration of potassium was subnormal in three of nine patients with APA. In patients with APA, administration of diuretics and salt restriction significantly elevated PRA. However, even under notable diurnal and day-to-day variations of plasma aldosterone concentrations, the aldosterone-PRA ratio was always elevated inappropriately (more than 400) in patients with APA. In contrast, after administration of diuretics, both the PRA and aldosterone levels increased significantly in patients with essential hypertension, but the aldosterone-PRA ratio was less than 200. Since the renin-angiotensin system seems to be a major factor controlling aldosterone secretion in normal subjects, it is suggested that an elevation of aldosterone-PRA ratio more than 400 is a useful screening tool for the prediction of APA among hypertensive patients. (Author abstract) (25 Refs)

98. MAJOR COMMON PROBLEMS. MANAGEMENT OF HIRSUTISM.

Chapman MG
Queen Charlotte's Maternity Hosp., London, England
Br J Hosp Med; 26(3):270-272 1981

Physiology, causes, diagnosis, and treatment of hirsutism which results from excess androgen secretion are discussed. Among the causes are androgen-secreting tumors, Cushing's syndrome, congenital adrenal hyperplasia, androblastoma, and teratoma. Changes in ACTH and cortisol concentrations, as well as increases in testosterone, urinary 17-ketosteroid, 17-hydroxycorticoid, and pregnanediol levels may indicate that hirsutism is of ovarian or adrenal origin. (10 Refs)

99. TAMOXIFEN IN BREAST CANCEROLOGY.

Bastit P
C.A.C. Henri-Becquerel, rue d'Amiens, 76038 Rouen Cedex, France
Gaz Med Fr; 88(30):4207-4208 1981

The use of tamoxifen (TX), an agent which selectively inhibits the action of estrogen on certain tissues, particularly the breast, in breast cancer therapy is discussed. TX (1-3 tablets, 10 mg/day) is used in the treatment of locoregional breast tumors. The rate of lesion regression (complete or greater than 50%) following TX treatment is approx 30%. TX is more effective against soft tissue involvement as compared with bony metastases. Some wk are often required for the appearance of TX therapeutic effects. TX is most effective when used in previously untreated patients and in those greater than 60 yr of age. Postmenopausal patients show a better response to TX than do premenopausal patients. Patient tolerance to TX treatment is generally good. Nausea and vomiting resulting from TX treatment is usually moderate, disappearing after several days or wk of treatment; flushing and amenorrhea may also result. Biologically TX causes a decrease in WBC and platelets. Hypercalcemia and liver disorders may also be observed. (no Refs) (In FRE)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STEROID HORMONE SYNTHESIS AND METABOLISM

1. EFFECTS OF 4-HYDROXY-4-ANDROSTENE-3,17-DIONE AND 10-PROPARGYLESTR-4-ENE-3,17-DIONE ON THE METABOLISM OF ANDROSTENEDIONE IN HUMAN BREAST CARCINOMA AND BREAST ADIPOSE TISSUES.

Perel E, Davis SP, Covey DF, Killinger DW
(c/o Killinger), Univ. Toronto, Medical Sciences Building, Rm. 7366, Toronto M5S 1A8, Canada
Steroids; 38(4):397-405 1981

The effects of 4-hydroxy-4-androstene-3,17-dione (4-OH-A) and 10-propargylestr-4-ene-3,17-dione (PED) on the aromatization of androstenedione (A) and the conversion of A to testosterone (T) were studied in incubations with breast carcinoma and breast adipose tissues. Parallel studies were carried out to determine the effects of 4-OH-A and PED on A metabolism in tissue from five patients with breast carcinoma. At 11 uM, both compounds fully inhibited aromatization, whereas the conversion of A to T was decreased in only two incubations. Studies with varying concentrations of 4-OH-A and PED demonstrated that both compounds inhibited estrone (E1) formation by 80% at a concentration of 0.085 uM, with max effect at 0.34 uM. 90% inhibition of estradiol (E2) formation was observed at inhibitor concentrations of 0.17 uM or greater. T formation was slightly affected at 0.67 uM, but was progressively inhibited with increasing 4-OH-A or PED concentrations, reaching 70% at 11 uM. Similar experiments with 4-OH-A in breast adipose tissue homogenates showed that a concentration of 0.1 uM was sufficient to inhibit aromatization while T inhibition required 11 uM. 4-OH-A and PED are selective inhibitors of aromatization in human breast tissues and may provide a mechanism for controlling estrogen responsive processes. (Author abstract) (32 Refs)

2. HORMONAL REGULATION OF ZINC METABOLISM IN A HUMAN PROSTATIC CARCINOMA CELL LINE (PC-3).

Giles PJ, Cousins RJ
(c/o Cousins) Dept. Food Science and Human Nutrition, Univ. Florida, Gainesville, FL, 32611
Cancer Res; 42(1):2-7 1982

Cells from a human prostatic adenocarcinoma cell line (PC-3) were maintained in M199 medium, with and without 5% Bobby calf serum, to examine aspects of cellular zinc metabolism. Cultures contained 0.5 to 1.0 x 10(6) cells/dish. Enhanced 65Zn accumulation in response to dexamethasone was observed after 24 hr in culture. the rate of efflux of accumulated 65Zn was not influenced by this hormone. Dihydrotestosterone had no effect on the accumulation of 65Zn by whole cells. Between 60 and 75% of the accumulated 65Zn was found in the cytosol (166,000 x g supernatant) fraction. Analysis of zinc distribution in cytosol by gel filtration chromatography revealed two major zinc-containing peaks, one comprised of high-mol-wt zinc-containing proteins and a low-mol-wt fraction that eluted identically to purified metallothionein (MT). Ion exchange chromatography of this low-mol-wt fraction resolved it into two components comparable to the major forms of MT purified from liver. Prior to differential 65Zn accumulation (12 hr), increased 65Zn was bound to the MT-like fraction in dexamethasone-treated cells and increased [35S]cystine was incorporated into this protein fraction. Other steroid hormones (dihydrotestosterone, hydrocortisone), as well as prostaglandin E2, resulted in an increased amount of bound 65Zn in the MT fraction, while estradiol and cortisone had no effect. Incubation of cells with actinomycin D or cycloheximide blocked the stimulatory effect of dexamethas one on the prostatic MT-like fraction. These experiments suggest that the MT genes are expressed in prostatic carcinoma cells. Moreover, they show that various aspects of prostatic zinc metabolism, particularly those related to MT, are influenced by certain steroid hormones, namely dexamethasone and dihydrotestosterone. (Author abstract) (33 Refs)

3. SHORT TERM ORGAN CULTURE OF HUMAN BREAST TUMOUR TISSUE AND ITS APPLICATION IN STUDIES OF STEROID METABOLISM.

Duncan JN, Davis JC, Wade AP, Walker S

Sub-Dept. Endocrine Pathology, Univ. Liverpool, Alder Hey Hosp., Liverpool L12 2AP, England

Eur J Cancer Clin Oncol; 17(10):1133-1142 1981

A method of organ culture capable of maintaining explants of human breast tumors for 3 days, as evidenced by comparison of the tumor histology before and after culture, is described. In general, survival was good, although cultures of scirrhous tumors were less successful. A commercial culture medium, Ham's F10, was used without serum addition but with the addition of insulin. Tumor tissue was cultured with 4-[14C]-cholesterol (11 cases), 4-[14C]-pregnenolone (3 cases) and 1beta,2beta-[3H]testosterone (3 cases). The existence of desmolase and aromatase enzyme systems in breast tumor tissue is suggested by the separation of neutral, acidic and phenolic fractions from cholesterol and pregnenolone cultures. Metabolites have not yet been identified. Further evidence of aromatase activity is given by the formation of [3H]-water from 1beta,2beta-[3H]-testosterone. (Author abstract) (31 Refs)

4. DETERMINATION OF TAMOXIFEN AND BIOLOGICALLY ACTIVE METABOLITES IN HUMAN BREAST TUMOURS AND PLASMA.

Daniel P, Gaskell SJ, Bishop H, Campbell C, Nicholson RI

Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Heath Park, Cardiff, CF4 4XX, Wales

Eur J Cancer Clin Oncol; 17(11):1183-1189 1981

This work describes the measurement of the antiestrogenic drug, tamoxifen, and two of its biologically active metabolites in the plasma and tumor tissue of patients with primary breast cancer. All three compounds were detected at high concentrations relative to those of estradiol, with which tamoxifen competes for binding to specific receptors in tumor cells. N-desmethyltamoxifen was the more abundant metabolite in both plasma and tissue, where its concentration exceeded that of the parent drug. An hydroxylated metabolite, metabolite B, was present at about 2% the concentration of tamoxifen in both plasma and tumors. The high concentrations of these compounds measured in human tissue were therefore similar to those previously found to be capable of preventing the specific binding of estradiol to its receptors in vitro. (Author abstract) (23 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

5. SERUM TESTOSTERONE LEVELS IN PATIENTS WITH ADVANCED PROSTATE CANCER DURING ANDRO GEN SUPPRESSION TREATMENT.

Fossa SD, Host H, Aakvaag A
Alminnelig avdeling, Det Norske Radiumshospital, Montebello, Oslon 3, Norway
Tidsskr Nor Laegeforen; 101(28):1570-1572 1981

The serum testosterone levels were determined in 52 patients with advanced prostate cancer with metastases 3 wk to 5 yr after the beginning of androgen suppression treatment. All patients were in the age bracket 51-79 yr. Surgical castration and diethylstilbestrol (DES) treatment (3 or 5 mg/day po) reduced the testosterone concentrations adequately to less than 2.8 nanomoles/liter in all patients thus treated. DES treatment with 2 mg/day caused a similar reduction of the testosterone level in 8/0 patients, but a dose of 1 mg/day caused such a reduction in 1/8 patients only. Polyestradiol phosphate (80 mg/mo im) was also unsatisfactory in most cases. The combination of this treatment with daily estrogen doses po (0.5-1 mg ethinylestradiol or 1-5 mg DES) reduced the testosterone levels adequately in 7/8 patients. The serum testosterone levels were determined again 6 wk to 2 yr later in 16 patients with progressive disease, who were estrogen-resistant. Surgical castration was performed in 9/16 cases, and the DES dose was increased to 3 mg/kg in the other 7. The serum testosterone dropped to below 2.8 nanomoles/liter in all patients who had higher values before the additional treatment. Clinical improvement (pain alleviation) was seen in 6/10 patients, but progression of the disease was seen in 1/10 patients despite a marked reduction of the testosterone level from 14.1 to 1.7 nanomoles/liter. Progression of the disease despite additional treatment was seen in the other 6/16 patients, in whom the testosterone levels were below 2.8 nanomoles/liter before the second test. (10 Refs) (In NOR)

6. SERUM PROLACTIN, ANDROGENS, OESTRADIOL AND PROGESTERONE IN ADOLESCENT GIRLS WITH OR WITHOUT A FAMILY HISTORY OF BREAST CANCER.

Boffard K, Clark GM, Irvine JB, Knyba RE, Bulbrook RD, Wang DY, Kwa HG
(c/o Wang) Dept. Clinical Endocrinology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England
Eur J Cancer Clin Oncol; 17(10):1071-1077 1981

Serum levels of prolactin, progesterone, estradiol, androstenedione and dehydroepiandrosterone sulfate have been measured in 52 adolescent girls with a family history of breast cancer and 90 girls without such a history. Using conventional statistical tests no significant differences were found in the endocrine status of the two groups. (Author abstract) (26 Refs)

7. PLASMA CONCENTRATIONS OF ESTRAMUSTINE PHOSPHATE AND ITS MAJOR METABOLITES IN PATIENTS WITH PROSTATIC CARCINOMA TREATED WITH DIFFERENT DOSES OF ESTRAMUSTINE PHOSPHATE (ESTRACYT(R)).

Gunnarsson PO, Forshell GP, Fritjofsson A, Norlen BJ
Res. Lab., AB Leo, Helsingborg, Sweden
Scand J Urol Nephrol; 15(3):201-205 1981

Plasma concentrations of estramustine phosphate and its major metabolites were measured in patients with prostatic carcinoma treated with increasing oral doses, 70-560 mg/day, of estramustine phosphate (Estracyt(R)). Parent drug and estradiol were measured by radioimmunoassay, and estramustine and its estrone analogue (Leo 271) utilizing gas chromatography. The concentrations of estramustine phosphate and estramustine were below or close to the limits of the methods. A linear correlation was found between the daily dose of estramustine phosphate, and plasma concentrations of Leo 271-the main metabolite - and estradiol, which suggests that no capacity limiting processes are involved in the pharmacokinetics of estramustine phosphate in man. Plasma was also analyzed during prolonged treatment with 560 mg/day. The metabolite pattern was not changed by 2 to 3 years of estramustine phosphate treatment. (Author abstract) (17 Refs)

8. LEYDIG CELL TUMOR WITH GYNECOMASTIA: HORMONAL EFFECTS OF AN ESTROGEN-PRODUCING TUMOR.

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J Clin Endocrinol Metab; 53(6):1291-1296 1981

A patient with a testicular interstitial cell tumor and gynecomastia is reported. The testicular tumor was capable of aromatizing 8.3% testosterone. Spermatic venous samples taken from the tumor-bearing side had marked elevations of 17beta-estradiol (E2), progesterone, and 17-hydroxyprogesterone (170 HP). The progesterone to 170HP and 170HP to androstene-dione ratios suggested and enzymatic block of 17alpha-hydroxylase and 17-20 lyase, possibly secondary to locally produced E2. The E2 produced by the tumor appeared to suppress gonadotropin secretion. The plasma testosterone and gonadotropin levels rose within 7 days after the removal of tumor, and the gynecomastia began to decrease. (Author abstract) (21 Refs)

9. SOME ASPECTS OF THE ENDOCRINE STATUS IN THE INFLAMMATORY BREAST CARCINOMA (MASTITIS CARCINOSA).

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Arch Geschwulstforsch; 52(1):67-73 1982

Endocrine parameters in 87 patients with inflammatory breast carcinoma (IBC) of rapid evolution (Group I) were compared with those in 400 patients with noninflammatory breast carcinoma (NBC) of normal evolution (Group II). Total urinary estrogens were measured in 81 patients from Group I and in 326 patients from Group II. Urinary 17-ketosteroids were measured in 60 patients from Group I and 61 patients from Group II. Mean age at menarche was significantly higher (14.8 +-0.22 yr) in Group I than in Group II (14.0 +-0.06 yr). Menarche at 16 yr or later occurred in 36.8% of Group I compared with 16.75% of Group II. Mean number of abortions was lower in Group I (1.72) than in Group II (2.16). Cases with no abortions were more frequent (48.1%) in Group I than in Group II (41.7%). Mean levels of urinary ethiocholanolone (Et) were low in Group I (0.66 +-0.04 mg/24 hr) than in Group II (1.04 +-0.08 mg/24 hr). The androsterone/Et ratio was higher (1.00) and the Et/11-oxygenated-17-ketosteroids ratio was lower (0.72) in group I than in group II (0.75 and 0.91, respectively). Results indicate a greater hormonal imbalance in IBC than in NBC. (49 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

10. CYTOSOL ESTROGEN AND PROGESTERONE RECEPTORS IN NORMAL AND PATHOLOGICAL TISSUES OF THE HUMAN UTERUS AND OVARIES.

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Ginekol Pol; 52(7):585-590 1981

Cytosol estrogen receptor (ER) and progesterone receptor (PR) levels were determined in normal and pathological tissues from endometria and ovaries. The samples were obtained from 30 women with normal endometrium, 20 women with normal myometrium, 10 women with normal ovaries, from 15 patients with endometrial carcinoma, 25 patients with uterine myoma, and 8 patients with ovarian neoplasms. The ER levels av (in femtomoles/mg) 193.4 in the follicular phase, 96.1 in the luteal phase, 166.7 in the climacterium (endometrium); 55.2 in the reproductive period and 49.3 in the climacterium in the myometrium, 22.1 in the normal ovaries, 160.6 in the patients with endometrial carcinoma (av age 62.2 yr), 104.5 in myoma (av age 43.9 yr), and 0-2,000 in ovarian neoplasms. The PR levels av 302.5 in the follicular phase, 125.2 in the luteal phase, 257 in the climacterium in the normal endometrium; 161.8 in the reproductive age and 121.4 in the climacterium in the normal myometrium; 67.1 in the normal ovaries; 131.5 (9-735) in endometrial carcinoma, 286 (0-705) in myoma, and 27-4,000 in ovarian neoplasms. The findings indicate the value of the determination of ER and PR levels in cytosol to evaluate the resistance of the target tissue to hormone therapy. (25 Refs) (In POL)

11. WHOLE-CELL UPTAKE AND NUCLEAR LOCALIZATION OF 1,25-DIHYDROXYCHOLECALCIFEROL BY BREAST CANCER CELLS (T47 D) IN CULTURE.

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Biochem J; 200(2):315-320 1981

Specific high-affinity receptors for 1,25-dihydroxycholecalciferol [1,25-(OH)2D3] have been described recently in broken-cell preparations of several cultured human breast cancer cell lines including the T47 D line. It was necessary to determine whether intact breast cancer cells in culture would bind 1,25-(OH)2D3 specifically and whether the next step in the proposed scheme of action, ie nuclear translocation, occurred. The following results were obtained. (1) Specific uptake of 1,25-(OH)2D3 by T47 D cells occurs in intact cells in culture. (2) The rate of uptake is proportional to medium 1,25-(OH)2D3 concentration but is slow compared with that of other steroid hormones, eg, estradiol, under identical conditions. Even at 0.5 nM-1,25-(OH)2D3 in the medium, at least 4 hr are required to reach max compared with less than 1 hr for estradiol binding. (3) Estimation of binding characteristics by Scatchard analysis indicates a single class of binding sites with Kd of 68 pM and 11,800 binding sites/cell, which are similar results to those obtained with broken-cell preparations. (4) Inclusion of various vitamin D metabolites in the incubation medium decreased specific binding of 1,25-(OH)2D3 by the intact cells in a manner identical with their effects in the broken-cell preparation and with potencies similar to their potency on Ca++ transport and bone resorption in vivo. Order of potency was 1,25-(OH)2D3 greater than (24R)-1,24,25-trihydroxycholecalciferol much greater than 25-hydroxycholecalciferol greater than (25R)-24,25-dihydroxycholecalciferol much greater than (25R)-25,26-dihydroxycholecalciferol. (5) In the 1,25-(OH)2D3-depleted state, 80% of the 1,25(OH)2D3 receptor is found in the cytosol fraction of the cells even when the subcellular fractionation is performed under low-salt conditions. By contrast after incubation with [3H]1,25-(OH)2D3, 59% of the specific 1,25-(OH)2D3 binding is found in the partially purified nuclei fraction. These data indicate that nuclear translocation of the receptor-hormone complex takes place in the intact T47 D cell. The results also support the hypothesis that the 1,25-(OH)2D3 receptor is functional in this cultured breast cancer cell line, which may provide a useful model for further study of the early biochemical events in 1,25-(OH)2D3 action. (Author abstract) (31 Refs)

12. PHYSICOCHEMICAL ANALYSIS OF REVERSIBLE MOLYBDATE EFFECTS ON DIFFERENT MOLECULAR FORMS OF GLUCOCORTICOID RECEPTOR.

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Biochem Biophys Res Commun; 103(1):60-67 1981

The use of molybdate to reversibly control pronounced alterations in the size and heterogeneity of glucocorticoid receptor proteins from a Syrian hamster melanoma is described. In the absence of molybdate, native glucocorticoid receptor from dexamethasone-sensitive tumors sediments at 7-8 Svedberg (SV) and 12-13 SV. Receptor isolated from dexamethasone-resistant tumors sediment at 7-8 SV only. Molybdate associated alterations in receptor size and heterogeneity can be induced by addition of molybdate to cytosol originally prepared in its absence. These molybdate alterations are reversible. In contrast to results obtained for the native cytosolic receptor, activated glucocorticoid-receptor complexes are resistant to molybdate induced changes in size. (20 Refs)

13. HORMONE RECEPTORS IN RENAL CELL CARCINOMA. THEIR UTILITY AS PREDICTORS OF RESPONSE TO ENDOCRINE THERAPY.

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Cancer Chemother Pharmacol; 6(2):151-154 1981

Estrogen (ER) and progesterone (PR) receptors were studied in 26 patients (22 men, 4 women; 36-84 yr old) with renal cell adenocarcinoma and results correlated with the responses of patients having measurable disease to hormonal therapy. Of the 26 patients, 25 had radical and 1 partial nephrectomy. Only 1/23 tumors assayed for ER had a significant receptor level (186 +-36 femtomole (fmol)/g tissue). Three of 24 tumors assayed for PR had significant titers (564 +-87, 484 +-87, 321 +-138 fmol/g tissue). In 11 tumors assayed, an av 32.4 +-13.3 mg cytosol protein/mg wet tumor tissue was found. Thus the ER+ tumor had a titer of approx 6 fmol/mg cytosol protein, while the highest PR titer was approx 17 fmol/mg cytosol protein. Only one patient had unsuccessful hormonal therapy prior to tissue sampling for ER and PR; the prior therapy could have diminished receptor titers. Ten patients who developed measurable metastatic disease subsequently were treated with hormonal therapy. In all but one, treatment consisted of high-dose progestational therapy administered either po or im. None showed any evidence of tumor regression during or after therapy. The data suggested that few, if any, renal cancers have high titers of ER or PR; those patients whose tumors have low receptor titers are unlikely to respond to hormonal therapy. (17 Refs)

14. PURIFIED GLUCOCORTICOID RECEPTORS BIND SELECTIVELY IN VITRO TO A CLONED DNA FRAGMENT WHOSE TRANSCRIPTION IS REGULATED BY GLUCOCORTICOIDS IN VIVO.

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Proc Natl Acad Sci USA; 78(11,part2):6628-6632 1981

Activated glucocorticoid receptor protein, purified to 40-60% homogeneity from rat liver extracts, binds selectively in vitro to a cloned fragment of murine mammary tumor virus (MTV) DNA. The DNA fragment tested contains about half of the sequences present in intact MTV DNA, and its rate of transcription, like that of the intact viral element, is strongly stimulated by glucocorticoids when it is introduced into the genome of a receptor-containing cell. In contrast, the receptor fails to bind selectively to DNA restriction fragments from E coli plasmids pBR322 and RSF2124 or from bacteriophages lambda and T4. Preliminary experiments to localize regions within MTV DNA responsible for selective binding have revealed thus far one subfragment that fails to bind the receptor and one selectively bound subfragment that maps far downstream from the 5' terminus of the normal RNA transcript. These studies are consistent with the notion that steroid receptors may modulate rates of transcription by recognizing specific DNA sequences within or near the regulated genes. (Author abstract) (35 Refs)

15. THE SPECIFIC BINDING OF ANDROGENS AND THE SUBSEQUENT DISTRIBUTION OF ANDROGEN-RECEPTOR COMPLEXES WITHIN MCF-7 HUMAN BREAST CANCER CELLS.

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Steroids; 38(4):439-452 1981

Using a whole cell suspension assay technique, we have examined both the specific binding of testosterone (T) and dihydrotestosterone (17beta-hydroxy-5alpha-androstan-3-one) (DHT) and the subsequent distribution of androgen binding activity within MCF-7 human breast cancer cells. We have observed that both androgens are bound with high affinity to the same single class of receptor which is present at a concentration of approx 8,000 sites per cell. The incubation of cells with either T or DHT was followed by the nuclear accumulation of specifically bound ligand which increased to max values within 1 hr and then decreased thereafter. However, only about 30% of the total cellular specific binding activity observed with either androgen was localized within the nuclear compartment at any time during a 4 hr incubation. Further examination of the extranuclear binding component suggested that a substantial portion of this activity was localized to the particulate fraction of the cytoplasm. The results of these studies suggest that both T and DHT are capable of exerting biological activity within MCF-7 cells, and raise the interesting possibility that androgen-receptor complexes may participate in the direct regulation of mitochondrial and/or microsomal function in this system. (Author abstract) (15 Refs)

16. EFFECTS OF ESTROGENS AND ANTIESTROGENS ON ESTROGEN RECEPTOR DYNAMICS AND THE INDUCTION OF PROGESTERONE RECEPTOR IN MCF-7 HUMAN BREAST CANCER CELLS.

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Cancer Res; 42(1):139-144 1982

Antiestrogens appear to be useful in the treatment of endocrine-responsive breast cancers in humans. We have examined the effects of estrogens (estradiol and diethylstilbestrol), and antiestrogens with a range of affinities for estrogen receptor (ER), on intracellular ER dynamics and biological response (progesterone receptor) induction in MCF-7 human breast cancer cells. The triphenylethylene antiestrogens studied are alpha- *p*-[*2-(1-pyrrolidino)ethoxy*]*phenyl* -4-methoxy alpha'-nitrostilbene (Cl628), alpha- *p*-[*2-(1pyrrolidino)ethoxy*]*phenyl* -4-hydroxy alpha'-nitrostilbene, cis- *3*-[*p-(1,2,3,4,-tetrahydro-6-methoxy-2-phenyl-1 naphthyl)phenoxy*]*-1,2-propanediol* , and cis-*3-*[*p-(1,2,3,4-tetrahydro-6-hydroxy-2-phenyl-1 naphthyl)phenoxy*]*-1,2,propanediol. The results indicate that: (a) ER translocation to the nucleus and progesterone receptor induction appear to be related to ligand affinity; (b) antiestrogens can differ substantially from one another in their dynamics of interaction with ER and in their abilities to stimulate increases in cellular progesterone receptor; (c) processing of ER by antiestrogens such as C1628 does not ensure subsequent induction of progesterone receptor; and (d) an apparently complex relationship exists between the presence and duration of hormone receptor complexes in the nucleus and the induction of progesterone receptor in MCF-7 cells. Since all four antiestrogens inhibit MCF-7 cell growth but differ in their ability to increase cellular progesterone receptor levels, these studies indicate that growth and progesterone receptor induction are phenomena that are independently modulated by antiestrogens in these human breast cancer cells. (36 Refs)*

17. TAMOXIFEN AND METABOLITES IN MCF7 CELLS: CORRELATION BETWEEN BINDING TO ESTROGEN RECEPTOR AND INHIBITION OF CELL GROWTH.

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Cancer Res; 42(1):317-323 1982

The binding of [3H]tamoxifen ([3H]Tam), a nonsteroidal antiestrogen, and of 4-[3H]hydroxytamoxifen ([3H]OH-Tam), a metabolite accumulated in vivo in target cell nuclei, was characterized in soluble extracts of human breast cancer MCF7 cells growing in a medium depleted in estrogens. Saturation analysis indicated a much higher affinity of OH-Tam (Kd = 0.15 nM) than for Tam (Kd = 4.8 nM). The binding of [3H]Tam and [3H]estradiol was competitive and mutually exclusive, and the binding site concentration (0.16 to 0.47 pmol/mg total protein) was similar for both ligands, strongly suggesting that antiestrogens were binding to the estrogen receptor (ER) in these cells. The ability of Tam and of some of its metabolites or derivatives to prevent the MCF7 cell growth was found to be correlated with their affinity for ER as determined by direct interaction or by binding competition with [3H]estradiol on the uterine and MCF7 cytosol ER. OH-Tam was the highest-affinity compound and was 100-fold more active than Tam. The inhibitions observed were actually due to Tam and OH-Tam, respectively, since we did not detect any significant metabolism of these two labeled compounds by the MCF7 cells. N-desmethyltamoxifen, the other Tam metabolite found in high concentration in human plasma, was as effective as Tam while cis-tamoxifen appeared less effective. Compound E, which has no lateral chain, was the only tested compound having a good affinity for ER and a poor efficiency in preventing cell growth. These results support the hypothesis that antiestrogens control the growth of breast cancer by acting directly on the ER located in cancer cells. (Author abstract) (33 Refs)

18. HORMONAL AND CYTOTOXIC CHEMOTHERAPY FOR ENDOMETRIAL CARCINOMA. STEROID RECEPTORS IN THE SELECTION OF APPROPRIATE THERAPY.

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Acta Obstet Gynecol Scand [Suppl]; (101):59-64 1981

Progestin therapy yields an objective remission in about one-third of patients with advanced endometrial carcinoma. Cytotoxic chemotherapy has also clearly proved effective in recent yr, and anti-estrogen therapy to an indicative degree. It is remarkable that both these therapies appear to exert their anti-neoplastic effect even in patients unresponsive to progestin. A survey of current knowledge on estrogen (ER) and progestin receptors (PR) demonstrates that they are present simultaneously in 41-80% of samples of endometrial carcinoma tissue. The concentration of cytosol ER and PR tends to decrease from well differentiated towards anaplastic carcinomas. This indirect evidence, together with some preliminary clinical observations, suggests that an absence or low concentration of ER and/or PR is suggestive of a poor prognosis. It is thought that an assay of ER and PR might be of value in predicting the response to chemotherapy in endometrial carcinoma, such as in breast carcinoma. This does indeed seem to be the case, as at least four independent clinical studies have to date confirmed that significant amounts of cytosol ER alone, and especially cytosol PR alone, or both together, in the tumor tissue can predict with reasonable accuracy a good sensitivity to progestin. In like manner, a low cytosol concentration of these steroid receptors appears to predict a good response to cytotoxic chemotherapy, as demonstrated in one study. Progestin and anti-estrogen exert their anti-neoplastic effect via an operative receptor mechanism in different ways, whereas cytotoxic chemotherapy acts by means not involving steroid receptors. It is therefore likely that a detailed characterization of the endocrine relations of the tumor by precise assay of ER and PR from the cytosol and nuclear fractions, together with determination of the end-product of progestin action, 17beta-hydroxysteroid dehydrogenase, will further enhance the accuracy of individual a priori selection of the most efficacious chemotherapy available. (Author abstract) (55 Refs)

19. A STUDY OF ESTROGEN AND PROGESTERONE CYTOSOL RECEPTOR CONCENTRATION IN BENIGN AND MALIGNANT OVARIAN TUMORS AND A REVIEW OF MALIGNANT OVARIAN TUMORS TREATED WITH MEDROXYPROGESTERONE ACETATE.

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Acta Obstet Gynecol Scand [Suppl]; (101):75-81 1981

ER and PR were assayed in 13 malignant and 20 benign ovarian tumors of different histologic types. ER was detectable in 67% and PR in 40% of the malignant tumors, compared with 35 and 45% in the benign tumors, respectively. The ER concentration was somewhat higher in the malignant lesions but there was no difference in the PR level. A retrospective review of 39 primary ovarian tumors of different pathologic stages and classes, treated postoperatively with medroxyprogesterone acetate (MPA, Depo-Provera, Upjohn) and in most cases Melphalan, showed a high Karnofsky performance index and good complete and partial response rates. The need for a prospective, controlled study of the role of MPA treatment of malignant ovarian tumors is evident. (Author abstract) (33 Refs)

20. STEROID RECEPTORS IN UROLOGICAL MALIGNANCIES.

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Acta Obstet Gynecol Scand [Suppl]; (101):87-92 1981

Within urological practice, three important types of cancer seem to be under endocrine influence or develop in endocrine-dependent organs: prostate cancer, hypernephroma and testicular tumors. Endocrine therapy is not used in testicular cancer, its value in renal cell carcinoma is limited, whereas it is a dominant form of therapy for prostate cancer. There seems to be a definite relation between androgen receptor content in primary prostatic carcinoma and response to hormonal manipulations. The presence of estrogen receptors is not well documented and probably the major effect of estrogen therapy is indirect, being exerted via the hypothalamo-pituitary axis. Progestin receptors are present in hyperplastic prostate as well as in prostate cancer and may indicate cases sensitive to progestin therapy. The assay method still needs considerable refinement before it can be introduced into clinical practice. (Author abstract) (65 Refs)

21. THE CYTOCHEMICAL DEMONSTRATION OF OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

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J Pathol; 135(3):237-247 1981

Presence of estrogen receptors (ER) in human breast carcinomas was examined. Eighty tissue samples from 79 patients (12 premenopausal and 67 postmenopausal) were studied by a cytochemical method involving two conjugation techniques (periodate and two-stage glutaraldehyde methods) to couple 17 beta-estradiol-6-O-carboxymethyloxime-bovine serum albumin with horseradish peroxidase. Compared with the 70% (56/80) detection rate of ER by the dextran-coated charcoal method (DCCM), 80% of samples (63/80) gave a positive reaction with the cytochemical method and all of those positive with the DCCM method were positive in the cytochemical study. Only seven samples were positive by histological examination. Nuclear staining was present in four samples. One was an infiltrating lobular carcinoma with few neoplastic cells and two were intraduct carcinomas. The periodate conjugation method led to a greater degree of coupling than the two-stage glutaraldehyde method even though a higher concentration was needed to demonstrate ER with the periodate method. Careful tissue preparation and handling are necessary for obtaining good results with the cytochemical method. (19 Refs)

22. ESTROGEN RECEPTOR QUANTITATION AND STAGING AS COMPLEMENTARY PROGNOSTIC INDICATORS IN BREAST CANCER: A STUDY OF 583 PATIENTS.

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Int J Cancer; 28(6):677-683 1981

Estrogen receptor (ER) quantity was measured at the time of primary diagnosis on 583 patients with breast cancer seen at the major treatment center in British Columbia between 1975 and 1979. Survival rates (overall, recurrence-free and post-recurrence) were assessed relative to ER concentration, staging, menopausal status, age, differentiation, and therapy. A linear trend in increased survival was demonstrable through variations in ER concentration from less than or equal to to greater than or equal to 260 fmoles/mg cytosol protein. This trend was highly significant and remained after adjustment for stage, menopausal status, and age, and was seen for all groups of patients except those with metastatic disease. The association of high ER concentration with increased recurrence-free survival was not due to differing response to adjuvant therapy, but the trend in post-recurrence survival was only significant in patients who had received hormonal therapy. Survival was as strongly associated with receptor concentration as with staging, and these two factors were almost completely independent. A proportional hazards model was fitted to produce predictions of survival, and showed that TNM Stage III patients with high ER concentrations have a better survival than Stage I or II patients with lower ER concentrations. This suggests that quantitative assessment of ER status is essential to definition of risk in breast cancer patients and that stratification in clinical trials and consideration for adjuvant therapy ought to be guided, in part, by a standardized ER-quantitative determination performed on the primary tumor. (Author abstract) (34 Refs)

23. GLUCOCORTICOID RECEPTORS AND SENSITIVITY IN LEUKEMIAS.

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Blut; 42(3):183-190 1981

Possible correlation between glucocorticoid receptor (GCR) determination and response to treatment in leukemias and lymphomas was studied. GCR determinations were made for leukemic cells from 46 adult leukemia patients and lymphocytes from 18 healthy controls. Leukemias included 17 acute nonlymphoblastic leukemias (ANLL), 4 acute lymphoblastic or undifferentiated leukemias (ALL/AUL), 3 blast crises, 15 chronic lymphocytic leukemias (CLL), and 7 leukemic malignant lymphomas (NHL). Normal lymphocytes expressed 2,312-6,856 GCR/cell (median 3,875). ANLL blasts had 0-15,295 GRC/cell (median 7,250). Two ALL/AUL patients with greater than 5,000 GRC/cell responded to combination therapy including glucocorticoids (GC); two ALL/AUL patients with less than 5,000 GRC/cell showed no response. CLL patients resistant to combination therapy including GC had generally lower GRC than responsive patients, indicating that GCR might have predictive value in CLL. No correlation was found between GCR and in vitro response to dexamethasone. No predictive value for GCR determination was indicated for nonlymphoid leukemias. (28 Refs)

24. THE UNEVEN DISTRIBUTION OF ESTROGEN AND PROGESTERONE RECEPTORS IN HUMAN ENDOMETRIUM.

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J Steroid Biochem; 14(10):997-1003 1981

Possible variations in the distribution of endometrial and cytoplasmic nuclear receptors during the menstrual cycle were studied. Accurately placed samples in five sections along the length of endometrium in uteri from 45 patients subjected to hysterectomy for benign conditions were used. Cytoplasmic estrogen (E2R) and progesterone (PgR) receptors were studied with (3H)-E2, (3H)-R5020, and dextran coated charcoal; the data were analyzed by the Scatchard technique. While endometrial E2R and PgR (measured as picomole (3H)-steroid bound/mg soluble protein) fluctuated during the menstrual cycle, a steep decrease from the fundal to the cervical sections which persisted throughout the cycle and after menopause was observed. The mean equilibrium dissociation constants (nanoM +- statistical error) of 0.22 +-0.02 and 2.42 +-0.18 for E2R and PgR, respectively, did not vary among the different sections, during the menstrual cycle or after menopause. Nuclear E2R and PgR, measured by a 'single point' assay, were measured as picomole (3H)-E2 or (3H)-R5020 bound/mg DNA. These nuclear E2R and PgR values were the reverse of the cytoplasmic values in all except the cervical section, and were highest in the lower uterus. The results may help explain the observed utility of E2R and PgR assays in breast cancer management and the lack of correlation in endometrial cancer. (25 Refs)

25. CHANGES IN SEX STEROID HORMONE RECEPTORS IN RAT UTERINE CYTOSOL DURING EXPERIMENTAL INDUCTION OF ENDOMETRIAL CARCINOMA.

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Nippon Sanka Fujinka Gakkai Zasshi; 33(6):757-766 1981

The sex steroid hormone receptor levels of uterine cytosol were assayed in the course of experimental induction of endometrial carcinoma in rats. The effects of administration of various hormones on the receptor levels were examined with each histological pattern of the endometrium. The dissociation constants for 17beta-estradiol and 17alpha,21-dimethyl-19-norpregna-4,9-diene-3,20-dione (R5020) binding with uterine cytosol were almost constant in spite of the various histological patterns of the endometrium. The influence of administered hormones on the receptor assay system could be counteracted by preincubation of uterine cytosol with dextran-coated charcoal 5x. Administration of diethylstilbestrol (DES) for 6 wk caused estrogen receptor levels to increase significantly in adenocarcinoma, while progesterone receptor levels did not show a tendency to decrease. Administration of mycophenolic acid (MPA) combined with DES did not cause a significant decrease in estrogen receptor levels in either atypical adenomatous hyperplasia or adenocarcinoma; progesterone receptor levels were decreased in all groups. Administration of MPA caused estrogen receptor levels to decrease significantly in adenocarcinoma. These data suggest that receptor levels can be controlled by the administration of sex hormones in the cause of development of endometrial carcinoma. (Author abstract) (36 Refs) (In JPN)

26. THE CORRELATION OF CYTOLOGIC GRADE AND STEROID RECEPTOR CONTENT IN EFFUSIONS OF METASTATIC BREAST CARCINOMA.

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Acta Cytol (Baltimore); 25(6):653-658 1981

The synthesis of estrogen receptor (ER) and progesterone receptor (PR) proteins by mammary carcinoma cells is a manifestation of biochemical differentiation. This study was an attempt to determine whether this acquisition of functional differentiation correlates with cytologic differentiation. Malignant effusions from 30 patients with mammary carcinoma were studied. ER and PR were measured by sucrose density gradient analysis. Membrane filters of the effusions were prepared, and a cytologic grade was assigned based primarily on nuclear size and nucleolar prominence. Ten cases were classified as well differentiated, 15 as moderately differentiated and 5 as poorly differentiated. Four of the 10 well-differentiated neoplasms contained greater than 7 fm/mg protein ER and PR. Six of the 15 moderately differentiated neoplasms contained significant levels of ER and PR. None of the five poorly differentiated neoplasms contained significant receptor. This study strongly suggests that there is a correlation between the cytologic grade and steroid receptor content in metastatic mammary carcinoma. In a prospective analysis of thin needle aspirations of breast cancers now underway, the nature of this relationship is being further defined. (Author abstract) (25 Refs)

27. ENDOCRINE ABLATION IN BREAST CANCER PATIENTS WHO HAVE FAILED CYTOTOXIC THERAPY.

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J Surg Oncol; 18(3):231-235 1981

Between 1972 and 1979, 46 women underwent endocrine ablative surgery, having failed combinations of chemotherapy, radiation, and surgery (including oophorectomy). All had clinically measurable disease; nearly half were afflicted with bone pain. Each was judged to be a candidate for the procedure by estrogen receptor studies (52%), response to L-dopa (39%), or response to prior oophorectomy (8%). All were followed to their death or to the present, with a minimum of 12 mo for those alive. Thirty-one (67%) were improved, and disease was arrested in 5 (11%) for a median time of 13.5 mo. There was no difference in response rates or intervals between estrogen receptor-positive and L-dopa-positive groups. Response was not correlated with disease-free interval or menopausal status. Best results were achieved in those with metastases confined to an organ system, particularly the skeletal complex. The procedure is withheld in those with brain metastases. Postablative chemotherapy appeared to prolong the control interval, though numbers are small. The low morbidity and mortality (1 death) of midline adrenaloophorectomy combined with the high incidence of recapture of disease leads us to recommend this procedure in appropriately selected patients who have previously failed other therapeutic modalities. (Author abstract) (9 Refs)

28. A STUDY OF DEXAMETHASONE RECEPTOR PROTEIN IN HUMAN GLIOMAS.

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Dept. Surgery, Kansas Univ. Coll. Health Sciences and Hosp., Kansas City, KS, 66103

J Surg Res; 31(6):447-455 1981

Glucocorticoids provide symptomatic relief when administered to patients with malignant brain neoplasms. Though improvement in peritumoral brain edema is thought to be the primary effect, a direct growth inhibitory effect of steroids cannot be ruled out. Available experimental data pertaining to the growth inhibitory effect of steroids are inconclusive. In this study we have attempted to reexamine this question by assaying the glucocorticoid receptor protein in the human glial neoplasms. Subject to certain constraints described in the study, glucocorticoid receptor protein is not detectable in the glial tumors. A critical analysis of the composite evidence obtained from clinical observations, and experimental studies suggest that glucocorticoids administered in the usual pharmacological doses have no direct growth inhibitory effect on human glial tumors. (Author abstract) (58 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

29. ALKALINE PHOSPHATASE PROTEIN INCREASES IN RESPONSE TO PREDNISOLONE IN HELA CELLS.

Hanford WC, Kottel RH, Fishman WH

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Biochem J; 200(2):461-464 1981

Quantification of term-placental alkaline phosphatase isoenzyme protein in HeLa TCRC-1 cells grown in the presence and absence of prednisolone indicates that there is a net increase in amount of enzyme-specific protein in prednisolone-stimulated cells. In a similar analysis of HeLa D98AH2 cells, prednisolone treatment causes the appearance of term-placental alkaline phosphatase protein and the loss of the intestinal isoenzyme protein. These results support the interpretation that the response of these cells to corticosteroids is the net accumulation of alkaline phosphatase protein rather than the modification of pre-existing enzyme to a more active state. (Author abstract) (26 Refs)

30. IMMUNOPRECIPITATION ASSAY OF ALPHA-FETOPROTEIN SYNTHESIS BY CULTURED MOUSE HEPATOMA CELLS TREATED WITH ESTROGENS AND GLUCOCORTICOIDS.

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Differentiation; 19(3):168-178 1981

This investigation was to study the biosynthesis of 3H-labeled alpha-fetoprotein (AFP) by cultured mouse hepatoma (HEPA-2) cells. Both the function and regulation of this oncodevelopmental gene are unknown. However, evidence indicates that mechanisms controlling the expression of AFP involve aspects of both normal embryonic development and neoplastic transformation. The secretion of AFP was analyzed during different phases of the growth cycle to provide information on AFP production using standard culture conditions.

the highest rate of secretion occurred during the stationary phase, followed by the late logarithmic and early logarithmic phases of growth, respectively. The production of AFP was then determined following the addition of glucocorticoids and estrogens in an attempt to understand hormonal factors that may be involved. Studies utilizing estradiol-17beta indicated that the secretion of AFP did not appear to be sensitive to this steroid even though sucrose density gradient analysis of HEPA-2 cytosol, for estrogenic receptors, revealed competitive binding moieties in the 8S and 4S regions of the gradient. In contrast, the secretion of the total complement of proteins, including AFP, was significantly stimulated by the glucocorticoids, dexamethasone and corticosterone. Analysis of HEPA-2 cytosol for glucocorticoid receptors revealed binding components in the 7S and 3-4S regions of the gradient. The 3H-dexamethasone bind ing appeared to be stereospecific since nonlabeled dexamethasone, but not nonlabeled estradiol-17beta, effectively displaced the bound radioactivity. The glucocorticoid-binding component in HEPA-2 therefore displayed characteristics reported for glucocorticoid receptors in normal liver and other hepatomas. (Author abstract) (69 Refs)

31. EFFECT OF ESTROGEN AND PROGESTERONE ON CELLULAR REPLICATION OF HUMAN BREAST TUMORS.

Dao TL, Sinha DK, Nemoto T, Patel J
Dept. Breast Surgery, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 42(1):359-362 1982

A total of 54 infiltrating carcinomas of the breast were studied for estrogen receptor concentration in the tumor cytosol and thymidine-labeling indexes. The results showed that there was no significant difference in the level of thymidine-labeling index between 22 primary and 32 metastatic breast cancers. No significant association between the levels of thymidine-labeling index and the presence or absence of estrogen receptors was observed. The effect of 'physiological' doses of estrogen and progesterone on cell proliferative activity was studied by the level of thymidine-labeling indexes in the tumor cells in 10 patients with multiple skin and sc metastases. Tumor biopsies were performed for labeling indexes both before and after hormonal treatment. The results showed that physiological doses of estrogen and progesterone induced a significant rise in thymidine-labeling index within 3 days after hormonal treatment in 7 of the 10 tumors. Of the seven tumors that showed a rise in thymidine-labeling index, three were estrogen receptor positive and four were estrogen receptor negative. Of the three nonresponsive tumors, one was estrogen receptor positive and two were estrogen receptor negative. The study suggests that estrogen and progesterone can induce cell replication in both estrogen receptor-positive and -negative tumors. (Author abstract) (18 Refs)

32. ACTION OF MPA IN ENDOMETRIAL ADENOCARCINOMA. CLINICAL RESULTS AND ULTRASTRUCTURAL AND HISTOCHEMICAL STUDY.

Pulle C, Rigano A
Istituto di Clinica Ostetrica e Ginecologica, Universita degli Studi di Messina, Messina, Italy
Minerva Ginecol; 33(10):937-954 1981

Of 113 endometrial adenocarcinoma patients, 36 (Group A) who were in Stage I and who had not received previous hormonal treatment were administered medroxyprogesterone acetate (MPA: 1 g/day, im) for 3 wk before surgery, 54 (Group B) who were in Stage I received the MPA (1 g/wk) immediately after surgery, and 23 (Group C) who were in advanced stages, and who could not have surgery received the MPA (1 g/dose) on alternate days up to 10 g, then 1 g/wk indefinitely. One-, 3-, and 5-yr survival rates were 36/36, 33/36, and 31/36, respectively, for Group A; 54/54, 46/54, and 41/54 for Group B; and 19/23, 15/23 , and 4/23 for Group C. Relapse rates after 1, 3, and 5 yr were 0/36, 2/36, and 4/36 for Group A; 4/54, 7/54, and 5/54 for Group B; and 4/23, 9/23, and 9/23 for Group C. Enzymatic and ultrastructural changes (cell apex, microvilli, ciliary apparatus, plasma membrane, cellular membrane, mitochondria, ribosomes, chromatin, desmosomal apparatus, cytoplasmic organelles, and nucleus) were observed in tumor cells of the patients who had been treated with MPA, indicating secretory activity in almost all of the cells; this activity was nearly absent in tumor cells of the untreated patients. The changes appeared to reveal an attempt of the neoplastic cell to return to normal cellular form and function. (58 Refs) (In ITA)

33. REMOVAL OF THE SURFACE-BOUND HUMAN CHORIOGONADOTROPIN RESULTS IN THE CESSATION OF HORMONAL RESPONSES IN CULTURED LEYDIG TUMOR CELLS.

Segaloff DL, Ascoli M
Div. Endocrinology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
J Biol Chem; 256(22):11420-11423 1981

The relationship between the binding and internalization of human choriogonadotropin and the stimulation of cAMP and steroid production was studied in cultured Leydig tumor cells. It was found that removal of the surface-bound hormone results in a rapid cessation of both cAMP and steroid production. We propose that the surface-bound hormone is responsible for the activation of steroidogenesis and that hormone internalization is involved in the deactivation of this process. (Author abstract) (17 Refs)

34. EFFECTS OF DES ON THE MORPHOLOGY OF THE LOBES OF THE BABOON PROSTATE.

Chai LS, Karr JP, Murphy GP, Sandberg AA
(c/o Sandberg) Div. Medicine, Dept. Health, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Invest Urol; 19(3):202-208 1981

Ultrastructural examination of the baboon prostate has revealed differences between the caudal and cranial lobes. The cranial epithelium is characterized by electron dense, tall columnar cells which contain numerous secretory vacuoles of homogenous appearance; the caudal epithelium is comparatively shorter in height and lighter in electron opacity. The caudal cells also contain numerous secretory granules which vary in their characteristics. After diethylstilbestrol (DES) treatment (5 mg per day for 3 wk), the tall caudal cells were reduced to a cuboidal shape; the number of secretory granules in these cells was also markedly reduced. In the cranial lobe, cell height was only moderately reduced, but the secretory vacuoles were decreased both in size and number. In addition, the fibromuscular stroma of the cranial lobe was greatly expanded after DES treatment, with an increased distance between adjoining acini being clearly noted. The systemic effects of DES on the baboons were noted by significantly (p greater than 0.02) elevated levels of serum sex hormone binding globulin and significantly reduced serum testosterone levels (p less than 0.01). (Author abstract) (31 Refs)

35. GRANULOCYTE TURNOVER IN ADVANCED HODGKIN'S DISEASE.

Prazmowska-Owczarek B, Hansz J
Klinika Hematologii A. M., ul. Skolna 8/12, 61-833 Poznan, Poland
Z Gesamte Inn Med; 36(18):678-680 1981

Granulocyte (GC) turnover was studied in 30 patients with Stage III or IV Hodgkin's disease (HD). Following hydrocortisone treatment the release of mature GC from bone marrow was lower in HD patients than in normal controls. Circulating and peripheral GC pools were the same in HD patients as in controls. Evidently GC turnover is a factor in abnormal immune response in HD. (8 Refs) (In GER)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

36. LEUKEMOGENIC EFFECT OF URETHANE ADMINISTERED TOGETHER WITH ESTROGENS TO MICE.

Bojan F, Gomba Sz, Kertai P
Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary
Egeszsegtudomany; 25(3):251-255 1981

Effects of carcinogenic and noncarcinogenic substances administered together with estrogens or urethane were studied in 6-8-wk-old male CFLP mice. Each substance was administered in three individual doses during an 18-day period, and the results were evaluated after 300 days. Lung tumors and lymphomas were found in the animals treated with ethyl formate (500 mg/kg), phenylurethane (100 mg/kg), pyrene (5 mg/kg), and their combinations with diethylstilbestrol (DES: 25 mg/kg), but there was no significant difference in the percentage of tumor-bearing animals between the treated animals and the untreated controls. Other groups were treated with dimethylnitrosamine (10 mg/kg), benzo(a)pyrene (5 mg/kg), or 3-methylcholanthrene (5 mg/kg), or their combinations with DES. There was no significant difference in tumor frequency between the groups treated with the carcinogens only and those treated with the carcinogens and DES. Solid tumors in the abdominal cavity and hepatic tumor were also found in addition to lung tumors and lymphomas in the DES-treated groups. Other groups were treated with urethane with or without BCG or Escherichia coli endotoxin (ET): the carcinogenic effect of urethane was not modified by BCG and ET. In other experiments, urethane induced multiple lung tumors with and without DES, but the number of lymphomas was significantly higher in the group treated with urethane and DES than in the groups treated with urethane or DES alone. (24 Refs) (In HUN)

37. SYNTHETIC CALCITONIN FROM SALMON IN THERAPY OF OSTEOLYTIC METASTASES DUE TO MAMMARY CARCINOMA.

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Clin Ter; 98(3):247-267 1981

Eighty-one mammary carcinoma (MC) patients (25-68 yr old; 79 women and 2 men) wi th osteolytic metastases were divided in two groups with one man in each group. In the first group 41 MC patients received calcitonin and radiotherapy (15), different protocols of polychemotherapy [(14 patients) adriamycin, vincristine, 5-fluorouracil, and endoxan], and 12 patients were given hormone therapy (suppressive or additive antiestrogens or high dose progesterone derivatives). Forty patients of the second group received radiotherapy 2500-3000 rads (15), chemotherapy (15), and hormone therapy (10). Clinical, biochemical, and radiologic evaluation was performed before, and 1, 3 and 6 mo after the start of therapy. Thirty-nine patients of the first group received calcitonin 20 days/mo for 6 mo, and 2 received calcitonin for only 2 mo. The decrease of pain occurred after first mo and persisted beyond 6 mo, regardless of type of treatment. Radiotherapy alone had the same effect, but of shorter duration and starting later (3 mo). Calcitonin had favorable effect on hypercalcemia and hypercalciuria. Osteolytic metastatic lesions were recalcified, but after 6 mo osteolysis reappeared in the same location. Further treatment was not effective. (27 Refs) (In ITA)

38. A CLINICAL STUDY OF PROSTATIC CANCER DURING 15 YEARS.

Miyazaki T, Momose S
Dept. Urology, Faculty Medicine, Kyushu Univ., Higashi-ku, Fukuoka 812, Japan
Nishinippon Hinyokika; 43(3):487-491 1981

For 15 yr, from 1965 to 1979, 84 patients with prostatic cancer were admitted and treated at the Department of Urology, Kyushu University. Recently, we traced the prognosis of, and performed clinical and statistical observations on the 84 patients. The incidence of prostatic cancer was 2.84% among male inpatients. The mean age of the 84 patients was 68.7 yr. About 90% of the chief complaints were related to micturition disorders. The stage of cancer was A in 6.0% of the patients, B in 16.7%, C in 35.7% and D in 41.7%. Acid phosphatase was elevated in 42.9%, 27.9% and 66.7% of all cases, nonmetastatic cases and metastatic cases, respectively. Fifty-one patients were treated by antiandrogen therapy, 6 by total prostatectomy, 19 by radiation therapy combined with antiandrogen therapy, and 7 with Estracyt(R), 1 patient received no anticancer therapy. The 5-yr survival rate was 60.8% for all cases, 67.9% for nonmetastatic cases and 47.8% for metastatic cases. Among the cases treated by antiandrogen therapy, the 5-yr survival rate was 63.8% for nonmetastatic cases and 37.3% for metastatic cases. The 5-yr survival rate was 55.4% for nonmetastatic cases treated by radiation therapy. (Author abstract) (17 Refs) (In JPN)

39. TAMOXIFEN VERSUS AMINOGLUTETHIMIDE IN ADVANCED BREAST CARCINOMA: A RANDOMISED CROSS-OVER TRIAL.

Smith IE, Harris AL, Morgan M, Ford HT, Gazet JC, Harmer CL, White H, Parsons CA, Villardo A, Walsh G, McKinna JA
Breast Unit, Royal Marsden Hosp., London SW3 6JJ, England
Br Med J; 283(6304):1432-1434 1981

Altogether 117 patients with advanced breast cancer were treated with either tamoxifen 10 mg by mouth bid or aminoglutethimide 250 mg by mouth 4x daily with hydrocortisone 20 mg bid in a randomized cross-over trial in which patients who failed to respond to the first treatment or relapsed while receiving it were switched to the other. Eighteen (30%) out of 60 patients initially treated with tamoxifen achieved an objective response and 11 (18%) showed stable disease. Seventeen (30%) out of 57 patients treated initially with aminoglutethimide achieved an objective response and 13 (23%) achieved stable disease. Objective responses in bone metastases were achieved more commonly with aminoglutethimide (11 patients (35%)) than with tamoxifen (5 (17%)). The predicted median duration of response for tamoxifen was 15 mo and for aminoglutethimide over 15 mo (no significant difference). Five (15%) out of 34 patients who failed to respond to tamoxifen and four out of six patients who relapsed after responding to tamoxifen subsequently responded to aminoglutethimide. In contrast, only 2 (6%) out of 31 patients who failed to respond to aminoglutethimide and none out of four patients who relapsed while receiving aminoglutethimide subsequently responded to tamoxifen. The main side effects occurring in the 97 patients who received aminoglutethimide as first- or second-line treatment were lethargy and drowsiness (36 patients) and rash (29); seven patients had to stop treatment because of side effects. In contrast, side effects were rare and mild with tamoxifen and no patient had to stop treatment because of them. Both tamoxifen and aminoglutethimide appear from this study to be equally effective in the medical endocrine treatment of advanced breast cancer. (Author abstract) (8 Refs)

40. THE COMBINATION OF MELPHALAN WITH PREDNISOLONE. ANTI-TUMOR EFFECT AND NORMAL TISSUE TOXICITY IN LABORATORY SYSTEMS.

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Cancer Chemother Pharmacol; 6(2):169-173 1981

The ability of prednisolone (PD) to improve the therapeutic index of melphalan (MP) was studied in a variety of laboratory systems. Clonogenic cell survival was measured for human melanoma xenograft HX34 in immune-deprived mice treated with MP alone or MP followed 4 hr later by PD (15 mg/kg). The ratio of MP doses required to produce similar levels of cell kill was 1.8. Cell survival measurements when PD was given simultaneously did not appear to differ from those when it was given with a 4 hr delay. Growth delay in the zenograft was greater when PD (4 hr delay or simultaneous) was added to MP than with MP alone (p less than 0.05). The survival of colony forming units (CFU) assayed by means of the agar diffusion chamber (ADC) from human bone marrow treated in ADC with MP or with a combination of MP and PD was determined. PD did not alter the survival of CFU-ADC after MP. When tumor cells were plated in ADC and treated in the same way as bone marrow cells, MP (10 mg/kg, iv) reduced the surviving fraction of tumor cells to 5.5 +-3 x 10(-3), while the addition of PD reduced the surviving fraction to 1.6 +-0.6 x 10(-3), a significant difference. No significant influence of PD on bone marrow repopulation following MP treatment was observed. No consistent influence of PD on gut microcolonies after MP treatment was observed, although a moderate effect cannot be excluded. When mice were given either 17 mg MP/kg alone or with 15 mg PD/kg, survival was significantly reduced if PD was added immediately (p less than 0.03) or 4 hr (p less than 0.001) after MP. The results support the view that steroids may enhance the anti-tumor effect of some alkylating agents, but the effect may be at the expense of increased normal tissue toxicity in some circumstances. (24 Refs)

41. LOBULAR CARCINOMA: ANATOMOPATHOLOGICAL AND CLINICAL ASPECTS.

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Radiol Med (Torino); 67(11):877-879 1981

The endocrine state of 5 lobular mammary carcinoma (LMC) patients was compared with that in 3 ductal mammary carcinoma (DMC) patients and 10 healthy women (HW). Av basal prolactin levels were 12.1, 9, and 12.8 nanog/cubic cm (cm3), respectively. After stimulation with sulpiride (100 mg im), the highest values of prolactin were 242.8, 108.7, and 128.1 nanog/cm3, respectively. The 17-beta-estradiol receptors in 4/5 cases of LMC had av value of 27.7 femtomole (fmt)/cc and in DMC had av value of 2 fmt/cc. Progesterone receptor levels were increased in only one case of LMC and in no DMC cases. Familial heredity was noted in four cases of LMC. Anatomopathological characteristics observed during mammography and dynamic telethermography of LMC are presented. On the basis of the data, therapy should consist of substances that will decrease prolactin secretion (2-alpha-Br-ergocryptine) and antiestrogens in cases where hormone receptors are present. (no Refs) (In ITA)

42. PERORAL ADMINISTRATION OF MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED CANCER OF THE BREAST. A PRELIMINARY REPORT.

Moller KA, Andersen AP

Radium Center, Municipal Hosp., DK--8000 Arhus C, Denmark

Acta Obstet Gynecol Scand [Suppl]; (101):47-48 1981

Medroxyprogesterone acetate (MPA: 500 or 1,000 mg/day) was administered po to 23 women (age 31-49 yr) with advanced breast cancer refractory to hormones and/or chemotherapy. Of the 19 patients evaluable after 2 mo of MPA therapy, 16 (84%) experienced subjective improvement (increasing appetite, increased mobility, and less pain). With 2 mo of treatment, 10 patients suffered disease progression and 3 were in a steady state. There were no complete responses, but 6 patients had a partial objective response (duration less than 4 mo to greater than 7 mo). (4 Refs)

43. INTERSPECIES RESPONSE TO CARCINOGENS AND OESTROGENS.

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Dept. Pharmacology, Coll. Medicine, Univ. Illinois Medical Center, Chicago, IL, 60680

Food Cosmet Toxicol; 19(5):607-610 1981

The response of a range of species (mouse, rat, hamster, guinea pig, rabbit, dog, monkey, and man) to estrogens are contrasted with those to carcinogenic chemicals. The response to a carcinogen is a general biological response obtained in a variety of species; the carcinogen induces its specific neoplastic effect in a high proportion of treated animals in a relatively short period of time. Although estrogens may produce an organ-specific effect in mice or rats, they do not produce the interspecies effect characteristic of a carcinogen. Effects of estrogens are strain- and species-dependent and thus do not demonstrate a carcinogenic profile. When a positive response is obtained, only a small proportion of treated animals is affected. In addition, clinical data do not demonstrate a relationship between estrogen administration and the occurrence of breast or cervical cancer. Estrogens are best described as having a nonspecific permissive action. (30 Refs)

44. HIGH-DOSE ESTROGEN THERAPY FOR ADVANCED PROSTATIC CANCER.

Koiso K, Ohtani M, Asakage H, Fujime M, Akima H, Kishi H, Kawabe K, Ueno A, Niijima T

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Jpn J Clin Oncol; 11(2):321-327 1981

Results of anti-androgen therapy given to 152 patients with Stage C and Stage D prostatic cancer are reported. Hexestrol (HX) was administered at doses of 30 or 100 mg daily. There was no statistical difference in changes in tumor size between the high-dose estrogen group and the low dose group in either Stage C or Stage D. HX was more effective in Stage C than in Stage D for decreasing the activity of acid phosphatase and alkaline phosphatase. High dose HX seemed to be effective in localizing bone metastases. There were no statistically differences in complete response, partial response, unchanged or progressive disease between high and low dose HX Stage C patients. No complete response was found in Stage D patients. Progressive disease was observed much more frequently in high-dose Stage C patients than in high-dose Stage D patients. No statistical differences were seen between the various groups in 5-yr-survival rates. Complications included painful gynecomastic, edema and hypertension. (13 Refs)

45. PRECANCEROUS AND EARLY STAGES OF ENDOMETRIAL CANCER.

Dallenbach-Hellweg G

Mannheim, W. Germany

Arch Gynecol; 232(1):22-32 1981

The genesis of precancerous and early stages of endometrial carcinoma and their prevention are discussed. The structural differences between endogenous and exogenous hormonal stimulation are described. Precancerous states develop in the endometrium on a background of continually elevated estrogen levels. The development of precancerous states can consequently be prevented by cessation of exogenous estrogen supply and neutralization of endogenous estrogens. (38 Refs) (In GER)

46. EXOGENOUS ESTROGENS AND BREAST CANCER.

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Am J Epidemiol; 114(5):710-713 1981

Rates of breast cancer at Group Health Cooperative of Puget Sound, Seattle, Washington, a health maintenance organization, remained stable from 1972-1979 in women aged 30-44 yr and in women aged 55-64 yr, despite the fact that the frequency of use of estrogen-containing drugs has varied substantially. By contrast, rates of breast cancer in women aged 45-54 yr appear to have fallen since 1977 in association with a substantial fall in estrogen use in women of this age group. The results are consistent with an etiologic role for current exogenous estrogen in breast cancer in middle-aged women. (Author abstract) (7 Refs)

47. EFFECT OF MEDROXYPROGESTERONE ACETATE AND DOXORUBICIN ON SUBLINES OF 13762 MAMMARY ADENOCARCINOMA IN RATS.

Formelli F, Zaccheo T, Casazza AM, Bellini O, Di Marco A

Instituto Nazionale per lo Studio e la Cura Dei Tumori, Via Venezian, 1, 20133 Milan, Italy

Eur J Cancer Clin Oncol; 17(11):1211-1221 1981

The 13762 mammary adenocarcinoma was subjected to serial transplantation in rats, freezing and thawing and in vitro cultivation. Following these procedures, various sublines were identified which differed in histological pattern, oncogenicity and sensitivity to medroxyprogesterone acetate treatment. Medroxyprogesterone acetate, administered sc at the dose of 100 mg/kg/day, 5 days/wk for 4 wk, delayed tumor onset and growth of sublines that had maintained their sensitivity to 17-beta-estradiol. Doxorubicin, administered iv at the dose of 3.6 mg/kg once a wk for 4 wk, was more active on the hormone-sensitive than on the hormone-insensitive subline. Simultaneous combined treatment for 4 wk with these agents caused higher growth inhibition than either single agent given alone. Other schedules of treatment were less effective. The following conclusions can be drawn: (1) the 13762 mammary tumor is heterogeneous, and hormone-sensitive or insensitive cell populations can be selected by simple manipulations; (2) there is no correlation between histological pattern and hormone sensitivity; (3) medroxyprogesterone acetate is active on sublines sensitive to 17-beta-estradiol treatment, but it also improves the activity of doxorubicin on hormone-insensitive sublines. (Author abstract) (22 Refs)

48. ESTROGEN INDUCED GROWTH OF HUMAN BREAST CANCER CELLS (MCF-7) IN ATHYMIC NUDE MICE IS ENHANCED BY SECRETIONS FROM A TRANSPLANTABLE PITUITARY TUMOR.

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Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824

Cancer Lett; 14(3):309-316 1981

The influence of pituitary hormones on growth of MCF-7 human breast tumor cells maintained in athymic nude mice was investigated. Sc injection of a pellet containing 17B-estradiol, and estrone in drinking water (0.5 mg/liter), resulted in sustained growth of the cells. Injection of a prolactin/growth hormone secreting rat pituitary tumor into the estrogen treated mice also caused growth of the tumor cells. No growth of tumor cells was observed in animals injected with pituitary tumor alone or in animals receiving neither pituitary tumor nor estrogen. Thus, rat pituitary tumor secretions enhanced the rate of in vivo MCF-7 tumor growth in estrogen treated animals, suggesting a synergism in their respective actions. (16 Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

49. CLINICAL ANALYSIS OF 24 CASES OF AUTOIMMUNE HEMOLYTIC ANEMIA.

Lu S
Dept. Internal Medicine, Shanghai Jingan District Central Hosp., Shanghai, Peoples' Republic of China
Zhonghua Neike Zazhi; 20(5):286-289 1981

Autoimmune hemolytic anemia (AHA) is caused by the production of autoantibodies that destroy the RBC of the patient. It can be classified into the primary and secondary types. Based on the temperatures required by the antibodies to act on RBC, AHA can be divided into two types, namely, the thermal antibody type (reactive at 37 C) and the cold antibody type (reactive at 4 C). Clinical findings are described for 24 cases of the thermal antibody type (9 males, 15 females; 15-80 yr old) treated between 1968 and 1978. Nineteen cases (79.1%) were primary AHA while 5 cases (20.9%) were secondary AHA due to systemic lupus erythematosus, acute infectious hepatitis, lymphatic reticulum cell tumor and chronic lymphocytic leukemia. The high incidence of primary AHA in this series differed greatly from those reported in world literature (eg 18.2%). Treatment was by administration of corticoids (eg prednisone) and immunosuppressive agents (eg cyclophosphamide) or by splenectomy. Prognosis was generally better in patients with primary AHA. (11 Refs) (In CHI)

GENERAL REVIEWS ON STEROID HORMONES

50. ANTIESTROGENS IN TREATMENT OF BREAST CANCER.

Gnatyshak AI
Medical Inst., Lvov, USSR
Vopr Onkol; 27(9):43-47 1981

The mechanism of therapeutic effect of antiestrogens (AEs) on breast cancer is reviewed. AEs reduce or alleviate the effect of estrogens on target tissues; the mechanism of their effect is associated with competitive interactions with estrogen receptors (ERs). Administration of the antiestrogen tamoxifen in combination with 17-beta-estradiol to rats bearing induced mammary gland carcinomas increased the concentration of ER and enhanced the activities of DNA-polymerase-B and RNA-polymerase-A. The antitumor effect of the tamoxifen was directly related to the concentration of ER. The tamoxifen was shown to be more effective in postmenopausal or early menopausal breast cancer patients than in premenopausal patients. Duration of remission depended upon the duration of administration of tamoxifen and, to a lesser extent, upon its dose. (40 Refs) (In RUS)

51. PRACTICAL APPLICATIONS OF IMMUNOCYTOCHEMISTRY TO THE PHARMACOLOGY AND TOXICOLOGY OF THE ENDOCRINE SYSTEM.

El Etreby MF
Res. Lab., Schering AG, Mullerstr. 170/178, D-1000 Berlin 65, W. Germany
Histochem J; 13(5):821-837 1981

Practical applications of immunocytochemistry in the investigation of endocrine glands and genital organs in pharmacologic and toxicologic studies are discussed. Using the immunoperoxidase technique and specific antisera, selective immunocytochemical staining can be localized in the various cell types found in the pituitary gland. Most hormones of the pars distalis and pars intermedia can be found in corresponding specific cell population. Diffuse hyperplasia and hypertrophy of either growth hormone or prolactin producing cells or both have been demonstrated immunocytochemically in the pituitarys of old dogs and estrogen and/or progestagen-treated Beagles. Using specific antisera and not labelled antibody peroxidase-antiperoxidase method, somatostatin was localized in a large population of immunoreactive neurons in the periventricular areas of the preoperative region and anterior hypothalmus of dogs. Using the immunoperoxidase technique and a specific antiserum against uteroglobulin, it has also been possible to localize specific staining in certain secretory cells of the rabbit endometrium in the preimplantation phase and after progesterone stimulation. Immunoreactive endogenous prolactin and growth hormone were detected in hyperplastic and neoplastic lesions of the dog prostate and mammary gland using the basic immunocytochemical procedure. Immunospecific prolactin and growth hormone staining was localized in different mammary tumors of the dog. Certain structural components of the mammary tumors, notably the myoepithelial elements and ductal epithelium, revealed predominant growth hormone-positive staining. These findings may explain the importance of growth hormone rather than prolactin in the pathogenesis of spontaneous and progestagen-related mammary tumors in the dog. (42 Refs)

52. CLINICAL AND LABORATORY FINDINGS AND RESULTS OF THERAPY IN 58 PATIENTS WITH ADRENOCORTICAL TUMORS ADMITTED TO A SINGLE MEDICAL CENTER (1951 TO 1978).

Bertagna C, Orth DN
Div. Endocrinology, Vanderbilt Univ. Medical Center North, Room A-4215, Nashville, TN, 37232
Am J Med; 71(5):855-875 1981

We reviewed 150 findings in 58 patients (14 males and 44 females) with adrenocortical tumors (26 with adenoma and 32 with carcinoma) admitted to Vanderbilt Hospital during 28 yr. In general, our findings agree with those reported by others in multi-institutional series or literature reviews. Adenomas took longer to diagnose than carcinomas. Adenomas usually caused Cushing's syndrome, but two caused virilization and three caused no endocrine syndrome. There was no difference in time required for diagnosis of carcinoma in men or women or in those with Cushing's syndrome, virilization or no endocrine syndrome. Urinary 17-hydroxycorticold (17-OHCS) levels were similar in those with adenoma and those with carcinoma, but 17-ketosteroid (17-KS) levels were usually less than 20 mg per day in patients with adenoma and greater than 20 mg per day in patients with carcinoma. Adenomas were uniformly independent of endogenous ACTH stimulation, but frequently responded to exogenous ACTH. As with adenomas, no carcinoma demonstrated normal suppression with dexamethasone or normal response to metyrapone, but only one responded to exogenous ACTH. Some patients had no clinical Cushing's syndrome despite high levels of plasma cortisol and urine 17-OHCS. 'Nonfunctional' tumors probably merely secreted insufficient steroids to cause signs and symptoms. Patients with adenoma were uniformly cured by surgical tumor resection. Occasional patients with carcinoma enjoyed long survival despite incomplete resection of their tumors, but most patients died of recurrent or metastatic carcinoma within 7 yr, often within a yr or two. Small tumor size and benign histologic features were insufficient to predict benign clinical behavior. The adrenocorticolytic drug, o,p'DDD, offered objective remission for only an occasional patient. (Author abstract) (37 Refs)

53. THERAPY OF ENDOMETRIAL ADENOCARCINOMA WITH SYNTHETIC PROGESTOGENS.

Lanza A, Fedele M, Renzetti ME, Ferraris G
II Clinica Ostetrica e Ginecologica, Universita di Torino, Via Ventimiglia, 3, 10126 Torino, Italy
Minerva Ginecol; 33(10):917-936 1981

Hormonal therapy (HT) of adenocarcinoma of the endometrium (E) was reviewed under the following headings: hormone receptivity of normal and pathologic E; different types of HT; precancerous lesions of the E and HT of such lesions, using synthetic progestogens; adjuvant HT; HT after surgery and irradiation; HT of advanced forms of the disease; secondary effects; mechanism of action of medroxyprogesterone acetate; and the HT protocol used at II Clinica Ostetrica e Ginecologica. (111 Refs) (In ITA)

54. BACKGROUND, DEVELOPMENT AND PROPERTIES OF PROGESTAGENS, WITH SPECIAL REFERENCE TO MEDROXYPROGESTERONE ACETATE (MPA).

Jeppsson S
Dept. Obstetrics and Gynecology, Malmo Allmanna Sjukhus, S--214 01 Malmo, Sweden
Acta Obstet Gynecol Scand [Suppl]; (101):7-10 1981

This review deals with the inhibitory effect of progestagens on pituitary gonadotropin release and endometrial proliferation and with the clinical use and side effects of 19-norsteroids and 17-OH-progesterone derivatives including medroxyprogesterone acetate. 17-OH-progesterone preparations are used without androgenic or estrogenic effects in the treatment of endometrial carcinoma; however, their use in oral contraceptives is no longer allowed in Sweden since they were found to increase mammary tumor incidence in beagles. (11 Refs)

55. UNOPPOSED ENDOGENOUS ESTROGENS AND THE INCIDENCE OF CANCER IN FEMALE REPRODUCTIVE ORGANS.

Johansson ED, Messinis JE, Nillius SJ
Dept. Obstetrics and Gynecology, Univ. Hosp., S--750 14 Uppsala 14, Sweden
Acta Obstet Gynecol Scand [Suppl]; (101):17-20 1981

Changes in the reproductive behavior (early menarche and late menopause, decline in number of pregnancies and live births, increases in sterile menstrual cycles) of women in industrialized nations and epidemiological studies linking the changes to breast, ovarian, and endometrial cancer are reviewed. The studies implicate unopposed endogenous estrogen production in the increased incidence of cancer of the reproductive organs and support the concept that use of progestins could halt this trend. (29 Refs)

56. DETERMINATIONS OF STEROID RECEPTORS AND THEIR CLINICAL APPLICATIONS.

Vihko R, Vierikko P
Dept. Clinical Chemistry, Univ. Oulu, SF--90220 Oulu 22, Finland
Acta Obstet Gynecol Scand [Suppl]; (101):21-28 1981

The distribution of steroid receptors in breast, endometrial, ovarian, prostatic, and renal carcinomas is described, and the usefulness of receptor determinations in therapy planning and in predicting responses to therapy is discussed. Methods of measuring receptor concentrations are described and compared. (88 Refs)

57. ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER.

Vihko R, Isotalo H
Dept. Clinical Chemistry, Univ. Oulu, SF--90220 Oulu 22, Finland
Acta Obstet Gynecol Scand [Suppl]; (101):29-35 1981

This review deals with measurements and properties of estrogen and progesterone receptors in human breast cancers, receptor frequency in primary and metastatic tumors and in pre- and postmenopausal patients, relationship between receptor status and serum hormone concentrations, receptor status and response to endocrine therapy, and receptor status as a prognostic factor both recurrence and survival. (67 Refs)

58. TREATMENT OF ADVANCED BREAST CANCER WITH PROGESTINS. A REVIEW.

Lober J, Rose C, Salimtschik M, Mouridsen HT
(c/o Mouridsen) Dept. RA-R 6, Finsen Inst., 49, Strandboulevarden, DK - 2100 Copenhagen O, Denmark
Acta Obstet Gynecol Scand [Suppl]; (101):39-46 1981

This paper reviews the theoretical background for the use of progestins in advanced breast cancer and the clinical experience obtained from 13 major studies. The av rate of response is about 30%, with somewhat higher rates when the dominant site of disease is localized to soft tissue and to bones, compared with viscera. Furthermore it seems that cross resistance between progestin therapy and other endocrine therapies is only partial. However, response rates related to previous therapy and to important prognostic variables such as age of the patient, disease-free interval and hormone receptor content of the tumor tissue are poorly elucidated. Only limited data are available concerning response rate in relation to dose and route of administration and data from prospective randomized trials to analyze these relations are still lacking. Considering the only modest side effects of treatment with progestins and the clinical and theoretical evidence favoring a mode of action different from that of other endocrine therapies, progestins are drugs with interesting qualities. Therefore future controlled studies with progestins alone or in combination with other systemic therapies should be carried out to establish the therapeutic efficacy of progestin therapy in primary and advanced disease. (Author abstract) (68 Refs)

59. CARCINOMA OF THE BREAST: PART 2, PROGNOSTIC FACTORS AND STAGING.

Elias EG
Oncology Program, Dept. Surgery, Univ. Maryland Hosp. and Sch. Medicine, 22 S. Greene St., Baltimore, MD, 21201
Md State Med J; 30(11):35-37 1981

Clinical and pathological staging of breast carcinoma is reviewed, with an emphasis on the prognostic role of clinical stage, histological grading, estrogen receptor status, carcinoembryonic antigen level, multicentricity of the primary tumor, age factors, concomitant obesity, sinus histiocytosis in the regional lymph nodes, and pregnancy. (22 Refs)

60. SURVEILLANCE AND MANAGEMENT OF HEREDITARY BREAST CANCER.

Lynch HT, Albano WA, Organ CH, Schmitz GD, Lynch JF
Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE
Breast; 7(4):2-9 1981

Clinical and biological characteristics of hereditary breast cancer are discussed to aid in establishing guidelines for its effective surveillance and management. Characteristics include significant early age of onset, excess of bilaterality and/or specific tumor associations, vertical transmission, and improved survival over nonhereditary forms. Recent observations suggest that a genetic linkage exists between breast cancer susceptibility and the glutamate-pyruvate transaminase locus in breast cancer prone families. Consistently lower plasma levels of prolactin, gonadotropin, estrone, and estradiol were measured in a high risk population, although the differences were not statistically significant. Oral contraceptives may act synergistically with other risk factors such as nutritional changes, alcohol usage, and increased cigarette smoking and may be primarily operative in familial breast cancer. Surveillance techniques include family counseling, monthly breast self-examination, biannual physician breast examination, mammography every 2 yr, and immediate biopsy of all dominant nodules. Existing breast cancers should receive standard evaluation and treatment, and the contralateral breast should be evaluated by mammogram and biopsy. The control of hereditary breast cancer could be aided immeasurably by the assembly of breast cancer prone kindreds in a carefully designed study. (35 Refs)

OTHER RELATED STUDIES

61. THE LACK OF ESTROGEN CONTROL OF RODENT ALPHA-FETOPROTEIN LEVELS.

Sheehan DM, Branham WS
Div. Teratogenesis Res., Natl. Center for Toxicological Res., Jefferson, AZ, 72079
Teratogenesis Carcinog Mutagen; 1(4):383-388 1981

The possible regulation of alphafetoprotein (AFP) by estrogens was investigated. Diluted plasma from adult mice fed diethylstilbestrol, estradiol, or control chow did not display any high affinity binding of estradiol, but did show nonsaturable low-affinity binding attributable to albumin. Plasma from 15-day-old rats bound estradiol with a KD = 0.5 x 10(-8) M. Daily injection of estradiol did not alter the plasma decay curve of AFP. Dissociation constants did not change with age or treatment with estrogens. The failure of estradiol to alter AFP levels was not due to a lack of biologically effective estrogen since the neonatal uterus showed a significant wt gain response under the same conditions. It was concluded that estradiol does not alter existing AFP levels in the neonatal rat. (39 Refs)

62. PRESENT AND FUTURE OF HORMONAL THERAPY IN METASTASIZED MAMMARY CARCINOMA.

Secreto G, Oriana S
Laboratorio di Ricerche Ormonali, Istituto Nazionale Tumori, Milano, Italy
Radiol Med (Torino); 67(11):867-870 1981

The androgenic activity was studied before ovariectomy in 133 patients (30-69 yr old; 17 in menopause) with advanced metastatic mammary carcinoma. In 18 normal women, av urinary excretion (ug/24 hr) of testosterone (Te) was 6.5 (0-12.7), and androstanediol (A) 35.0 (7.2-56.5). The 133 patients were divided in three groups. Group 1 had 61 patients with Te and A in the normal range. Group 2 had 46 patients with Te or A or both above normal. Group 1 and 2 were treated only by ovariectomy (OX). Twenty-six patients in Group 3 had 26 patients with excretory androgens above normal, after OX and repeated androgen determinat ions, were treated with dexamethasone (DXM) in repeated cycles (1.5 mg/day for 30 days) every time Te or A were above normal. Values of excretory androgens were reduced after OX, but in groups 2 and 3 they were always well above normal values. Bone metastases (Me) were prevalent in groups 2 and 3, while those in group 1 had Me mostly in viscera and soft tissue. Histological examination of resected ovaries was performed in 59 cases and in 40 hyperplasia was present. Remissions after OX were observed in 16 cases (26%) of group 1, and 25 (54.3%) of group 2. Highest response was seen in group 3, 24/26 (92%); 12 in this group showed improvement before DXM treatment. Av remission time was shortest for group 1, and longest for group 3. One patient in group 1 was in remission after 39 mo, 5 in group 2 after 12-84 mo, and 8 in group 3 after 17-94 mo. The excretory urinary androgens can indicate response to OX and usefulness of DXM treatment. (5 Refs) (In ITA)

63. MEDROXYPROGESTERONE ACETATE (MPA) PLASMA LEVELS AFTER ORAL AND INTRAMUSCULAR ADMINISTRATION IN A LONG-TERM STUDY.

Hesselius I, Johansson ED
Dept. Gynecological Oncology, Univ. Hosp., S - 750 14 Uppsala 14, Sweden
Acta Obstet Gynecol Scand [Suppl]; (101):65-70 1981

In a long-term study (1 yr) the plasma concentration of medroxyprogesterone acetate (MPA, Depo-Provera, Provera, Upjohn) was measured in 30 patients with endometrial carcinoma treated with MPA in the following dosages: (1) MPA 1,000 mg im weekly, (2) MPA 1,000 mg im once every second wk, and (3) MPA 100 mg po bid. In the orally treated group the blood samples were taken just before the next tablet. The plasma concentration in the orally treated group rapidly reached steady state, while the im treated group showed gradually increasing levels that had a tendency to level off after 6 mo. The mean concentration at the end of the yr was about 3x higher for MPA 1,000 mg im weekly than for MPA 100 mg po bid. This does not take into consideration the peak MPA level that occurs 2-4 hr after each tablet. MPA im has a very good depot effect, with release of MPA from the injection site for up to 9 mo. The steady initial increase in MPA plasma concentration seen in the im treated groups is probably due to the additions of new depots rather than accumulation in the body generally. (Author abstract) (13 Refs)

64. PHARMACOKINETICS OF MEDROXYPROGESTERONE ACETATE ADMINISTERED BY ORAL AND INTRAMUSCULAR ROUTE.

Lober J, Mouridsen HT, Salimtschik M, Johansson E
Dept. R A, Finsen Inst., DK - 2100 Copenhagen, Denmark
Acta Obstet Gynecol Scand [Suppl]; (101):71-74 1981

The present study was undertaken to elucidate: (1) The relationship between plasma concentration of medroxyprogesterone-acetate (MPA, Clinovir(R), Depo-Provera, Upjohn) administered both po and im. (2) The relation between dose and plasma concentration of MPA. Nineteen patients entered the study. In each patient the plasma concentration was monitored after the administration of a single oral and one im dose of MPa at the following dosage levels: 100 mg (5 patients), 400 mg (5 patients), 800 mg (5 patients) and 1,200 mg (4 patients). The interval between the oral and im administration was 1 wk. The results show: (1) A very large interindividual variation in plasma concentration. (2) An increase in plasma concentration after both oral and im dose. (3) After the im administration, plasma levels remained steady or increased slightly throughout the test period. (4) After the oral administration the concentration increased rapidly to reach a peak by 2-7 hr, subsequently decreasing. Peak concentrations were 2-10x higher than after im administration. (5) Over the test period, the plasma concentration x time (0-168 hr) is similar in the two modes of administration. (Author abstract) (4 Refs)

65. TESTOSTERONE AND HIGH DENSITY LIPOPROTEINS IN PATIENTS WITH DISSEMINATED GASTRIC CANCER.

Higuchi T, Nakamura T, Uchino H

Dept. Internal Medicine, Shiga Center for Adult Diseases, 328 Moriyama, Moriyama, Shiga 524, Japan

Jpn J Clin Oncol; 11(2):329-333 1981

The plasma testosterone and serum high density lipoprotein profiles of 13 male patients with newly diagnosed, histologically proven disseminated gastric cancer, and seven male patients with histologically proven hepatic cirrhosis were compared to those of healthy controls. Mean albumin level in patients with hepatic cirrhosis and gastric cancer was significantly lower than that in control subjects. Mean total bilirubin in both cirrhotic and gastric carcinoma patients was significantly higher than in controls, as were levels of alkaline phosphatase. Mean high density lipoprotein-cholesterol (HDL-C) levels in cirrhotic and gastric carcinoma patients were significantly lower than those in controls. Mean plasma testosterone levels in patients were also lower than those in controls, but the differences were not significant. A significant positive correlation was observed between HDL-C levels and testosterone levels in gastric carcinoma patients. Gastric carcinoma patients with lower testosterone levels (5.0 nanomol/ml) had significantly lower HDL-C and serum albumin levels than similar patients with higher testosterone levels. Significant correlation was observed between serum levels of HDL-C and survival time, and between plasma levels of testosterone and survival time. (15 Refs)

66. LONG-TERM EFFECTS OF ENDOCRINE TREATMENT ON SERUM PITUITARY HORMONES IN ADVANCED PROSTATIC CARCINOMA PATIENTS.

Lukkarinen O, Hammond GL, Kontturi M, Vihko R
Dept. Surgery, Univ. Oulu, Oulu 22, Finland
Scand J Urol Nephrol; 15(3):207-211 1981

Peripheral serum concentrations of FSH, LH, prolactin and ACTH were measured in 22 patients with advanced prostatic carcinoma treated by castration, polyestradiol phosphate (Estradurin(R)) administration and a combination of castration and Estradurin(R) administration during the first 12 months of treatment. Estradurin(R) treatment alone (80 mg im once a month) did not result in any significant changes in the circulating concentrations of FSH, LH and prolactin. Therefore, the clear-cut inhibition of testicular steroidogenesis observed under this kind of treatment does not appear to be due to an inhibition of pituitary gonadotropin secretion, and is most likely due to a direct estrogen effect on Leydig cells. Castration led to grossly elevated serum FSH and LH levels. In this group, serum FSH remained at a high level, whereas LH was close to pretreatment levels 9 months after castration, suggesting differences in pituitary capacity to secrete FSH and LH under these conditions. Concentrations of circulating FSH, and to a lesser extent LH, in the combination treatment group were between those found in the castration and estrogen-only treatment groups, suggesting that the secretion of both gonadotropins can be suppressed by estrogen. No changes in serum prolactin and ACTH concentrations were seen in the three treatment groups. (Author abstract) (21 Refs)

67. RESIDUAL ADRENOCORTICAL FUNCTION AFTER BILATERAL 'TOTAL' ADRENALECTOMY FOR CUSHING'S DISEASE.

Chalmers RA, Mashiter K, Joplin GF
(c/o Joplin) Endocrine Unit, Dept. Medicine, Royal Postgraduate Medical Sch., Hammersmith, London W12 0HS, England
Lancet; 2(8257):1196-1199 1981

Six patients who had been treated for pituitary-dependent Cushing's syndrome by intended complete removal of the adrenal glands are described. There were clinical grounds for attempting to reduce maintenance steroid therapy in each case, and it was found possible to withdraw steroids completely without adverse effects. These findings illustrate the importance of clinically assessing the minimum steroid requirements of adrenalectomized patients and the need for continued surveillance for persistent or recurrent Cushing's syndrome. (Author abstract) (21 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. CHOLESTEROL ESTER METABOLISM IN PLASMA DURING ESTROGEN AND ANTIANDROGEN TREATMENT IN MEN WITH CARCINOMA OF THE PROSTATE.

Wallentin L, Varenhorst E
Dept. Internal Medicine, Linkoping Univ., S-581 85 Linkoping, Sweden
J Lab Clin Med; 98(6):906-916 1981

The male predominance in atherosclerotic disease has been ascribed to differences in lipid and lipoprotein metabolism between men and women. The influences of estrogen and antiandrogen treatment on the cholesterol ester metabolism and lipoproteins in plasma in men were therefore studied. Forty -six men with carcinoma of the prostate were studied before and after 2 and 8 wk treatment with either polyestradiol phosphate and ethinyl estradiol or orchidectomy or the testosterone receptor-blocking gestagenic drug cyproterone acetate. The estrogen treatment increased the HDL-TC and the level of TGs in HDL and LDL and reduced the TC and LDL-TC simultaneously with elevations of the fractional and molar cholesterol esterification rates. Orchidectomy caused only slight elevations of the TC level and the molar cholesterol esterification rate. Cyproterone acetate reduced the TC, LDL-TC, and HDL-TC concentrations simultaneously with an increase in the fractional cholesterol esterification rate. The alterations of TC and LDL-TC were positively correlated to the changes in the molar cholesterol esterification rate and negatively correlated to the alteration in the fractional cholesterol esterification rate. High doses of estrogen appeared to raise the TG level and the production of CE in plasma. Both estrogen and cyproterone acetate therapy lowered the LDL-TC level simultaneously with a raised fractional elimination of unesterified cholesterol as CEs from plasma. Although the testosterone production was practically eliminated by all three forms of treatment, there was no one change of plasma lipoproteins common to all three groups. Therefore the lower estrogen level rather than the higher testosterone level might cause the lower HDL levels in men compared to women. (Author abstract) (36 Refs)

2. EFFECTS OF HYPOCHOLESTEROLEMIA AND CHRONIC HORMONAL STIMULATION ON STEROL AND STEROID METABOLISM IN A LEYDIG CELL TUMOR.

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J Lipid Res; 22(8):1247-1253 1981

The studies presented herein were done to investigate the effects of drug-induced hypocholesterolemia and chronic hormonal stimulation on cholesterol metabolism and steroid biosynthesis in a functional Leydig cell tumor. It was found that 4-aminopyrazolo(3,4-d)-pyrimidine (4-APP)-induced hypocholesterolemia had no effect on (a) the amount of cholesterol present in the tumor, (b) cholesterol biosynthesis, and (c) steroid production. Chronic stimulation with choriogonadotropin also had no effect on the amount of cholesterol present in the tumor, but it increased steroid production and cholesterol biosynthesis. These results suggest that the Leydig tumor cells primarily use intracellular cholesterol for steroid biosynthesis. Other data show that 4-APP treatment reduces gonadotropin binding in the Leydig tumor cells. (Author abstract) (28 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

3. STUDIES ON ADRENAL ANDROGEN IN PATIENTS WITH PROSTATIC CARCINOMA RECEIVING ENDOCRINE THERAPY.

Iwasaki A
Dept. Urology, Yokohama City Univ. Sch. Medicine, Yokohama, Japan
Nippon Hinyokika Gakkai Zasshi; 72(6):701-716 1981

Plasma 4-androstenedione (4-A) was measured in 29 normal subjects (10 men 24-27 yr old, 10 women 23-26 yr old, 9 men 60-67 yr old), in 21 patients with prostatic hypertrophy, in 9 untreated patients with prostatic cancer, and in 51 patients treated with hormone therapy for prostatic cancer. Effects of adrenal androgens on reactivation of prostatic carcinoma were studied with 4-A as a marker. Av 4-A levels were 81 +-38 nanog (ng)/deciliter (dl) in the 10 normal men, 105 +-22 ng/dl in the 10 normal women, and 73 +-28 ng/dl in the 9 aged men. No significant differences were observed between 4-A levels at 9 am and at 5 pm, but the 9 am levels were higher. Compared to the aged men, 4-A levels were not significantly different in the patients with prostatic hypertrophy and in those with prostatic cancer. Plasma 4-A, testosterone, and cortisol, concentrations of intratesticular testosterone, and steroidogenesis in resected testicular tissue were studied in 94 patients treated for 2 mo to 9 yr with Hexestrol (HE; 30 mg/day) or chlormadinone acetate (CMA; 100 mg/day). Plasma levels of cortisol were markedly increased due to estrogen therapy. Steroidogenesis was completely blocked in testicular tissue after administration of HE for 2 mo, an intratesticular testosterone concentrations were markedly decreased after administration of CMA for 2 mo. 4-A levels were av 52.9 +-20.0 ng/dl in patients treated for 9 yr with HE and were av 49.9 +-20.9 ng/dl in patients treated with CMA. Reactivation of prostatic cancer due to adrenal androgens was thought to be unlikely. (50 Refs) (In JPN)

4. PLASMA PROLACTIN LEVELS IN PATIENTS WITH BREAST CANCER.

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Cancer; 48(12):2687-2691 1981

The plasma prolactin levels of 98 healthy women 22 to 65 years old showed a strong inverse correlation with age. This relationship persisted for older premenopausal and postmenopausal women (aged 30 to 65 years) whose results were compared with those of 34 premastectomy early breast cancer patients, another 38 studied 4 to 6 weeks after mastectomy, and 38 with advanced disease (age range, 30 to 77 years). There was no correlation between age and plasma prolactin in any of the breast cancer groups. When patients and controls were classified according to their menopausal status, the premastectomy and postmastectomy early breast cancer groups both showed significantly higher prolactin concentrations than the corresponding controls (p less than 0.001 in all cases). These abnormalities were particularly prominent in the patients studied after surgery, although the difference was significant only for the postmenopausal groups (p less than 0.05). Plasma cortisol and urinary free cortisol levels were normal in postmastectomy patients , suggesting that stress was not the cause of elevated prolactin levels. In advanced breast cancer, elevated plasma prolactin concentrations were found only in the postmenopausal patients. (Author abstract) (32 Refs)

5. HORMONE REGULATION OF DNA SYNTHESIS OF NORMAL AND HYPERPLASTIC HUMAN BREAST TISSUES IN VITRO AND IN VIVO (MEETING ABSTRACT).

Welsch CW
Department of Anatomy, Michigan State University, East Lansing, MI, 48824
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A3 1981

The hormones analyzed in these studies were bovine insulin (5.0 ug/ml), ovine prolactin (5.0 ug/ml), human prolactin (5.0 ug/ml), human placental lactogen (5.0 ug/ml), human growth hormone (5.0 ug/ml), 17beta-estradiol (0.001 ug/ml) and progesterone (1.0 ug/ml). Epithelial (ductal) DNA synthesis of the cultured human breast tissues was significantly stimulated by insulin, human prolactin, human placental lactogen and 17beta-estradiol; ovine prolactin, human growth hormone and progesterone were without a stimulatory effect. The original morphology of the explants was maintained. In vivo studies (athymic nude mice): Human breast tissue was obtained and processed as described above and transplanted sc (dorsal) to 8 wk old female athymic nude mice (Balb/c). Thirty days after transplantation, the mice were treated with the following hormones: human placental lactogen (0.5 mg; 2 x daily); estrogen (17beta-estradiol, 1.0 ug, 1 x daily and estrone in drinking water, 0.5 mg/liter) or a sc grafted rat pituitary tumor (RPT) which secretes copious quantities of prolactin and growth hormone (host mice blood rat prolactin levels, greater than 4000 ng/ml). After 30 days of hormone treatment, the grafted human breast tissues were excised and incubated for 4 hr in a 3H-thymidine enriched culture media. The grafts were processed for 3H-thymidine autoradiography. Human placental lactogen, estrogen and estrogen + RPT significantly stimulated DNA synthesis of the ductal epithelium of the grafted human breast tissues; RPT alone was ineffective. One hundred percent of the grafts were accepted by control or hormone treated mice; no sign of immunological rejection was observed. The grafts acquired the host blood supply and retained the original morphology. The relative merits of our in vitro and in vivo systems for the study of human breast tissues will be discussed. (no Refs)

6. HORMONE LEVELS IN HUMAN BREAST CYST FLUID (RELATIVE PLASMA CYST FLUID LEVELS) AND STUDIES ON THE MECHANISM OF ENTRY OF HORMONES INTO BREAST CYSTS (MEETING ABSTRACT).

Bradlow HL, Schwartz MK, Fleischer M, Rosenfeld SS, Kream J, Breed CN, Fracchia AA
Rockefeller University, Memorial Sloan-Kettering Cancer Center, New York, NY
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A4 1981

Cyst breast disease is a common occurence in women from age 35 to menopause. Although breast cysts are not precancerous per se, repeated studies over many yr have reported and increased risk for breast cancer in women with breast cysts when compared to normal controls. As part of a program to explore the possible relationship between the unusual hormone levels found in breast cyst fluid and the incidence of breast cancer, the concentration of a wide variety of hormones in breast cyst fluid were determined and compared with the plasma levels of these same compounds. Hormone levels were measured in cyst fluid from 1046 women who were then followed to determine breast cancer incidence. Both peptide and steroid hormones were measured in cyst fluid and in blood samples obtained simultaneously. The peptide hormones measured were luteinizing hormone (LH), follicle stimulating hormone (FSH), human prolactin (HPrL) and beta human chorionic gonadotropin (beta HCG). The first two compounds were present in cyst fluid in concentrations at or below plasma concentrations. HPrL and betaHCG however, were present in cyst fluid at concentrations greater than the plasma concentration in most of the patients studied. The cyst/plasma ratio ranged from only slightly greater than 1 to 200-fold. No correlation was found between the magnitude of the HPrL level and the betaHCG levels. The steroids studied were cortisol (F), testosterone (T), dihydrotestosterone (DHT), progesterone (P), estradiol (E2), estrone (E2), dehydroisoandrosterone (D), androsterone (A), and the sulfates of the latter four compounds. F, T, P. DHT, E1 and E2 were not significantly elevated in cyst fluid over plasma levels. D, A, DS, AS, E1S and E2S all showed elevated cyst fluid/plasma ratios, indeed in some cases as much as several thousand-fold greater than . Levels of DS and AS were as high as 20000 ug/dl. E1S and E2S were also markedly elevated in cyst fluid. (no Refs)

7. FECAL STEROID EXCRETION IN BENIGN BREAST DISEASE - SIMILARITIES TO BREAST CANCER (MEETING ABSTRACT).

Papatestas AE, Miller SR, Panveliwalla D, Aufses AH
Department of Surgery, Mount Sinai School of Medicine, New York, NY
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A19 1981

The observed association between benign breast disease and breast cancer risk suggests a possible common etiologic mechanism. Fecal steroid levels have been linked to breast cancer risk through enhancement of estrogen synthesis from cholesterol metabolites. We have measured fecal steroids in women with breast cancer (cases) and in control women with or without benign breast disease (BBD). The former control group includes women with fibrocystic disease, intraductal papillomas, sclerosing adenosis and fibroadenomas. Three fecal specimens per patient were collected at the time of diagnosis and treatment, and the mean steroid value was evaluated. Determination of steroid levels in mg/g dry wt was made by the methods of Grundy and Miettinen. Comparison of the mean excretion of fecal steroids between controls with or without benign breast disease and cases, using analysis of variance showed significant differences for all neutral steroids but not for acidic steroids. The results indicate that women with benign breast disease have increased excretion of fecal steroids similar to that of cases but significantly higher than that of the remaining controls. T test for differences between groups (1) and (2) for total fecal steroids (TFS) equals p less than 0.01, for total neutral steroids (TNS) equals p less than 0.02, for first NS equals p less than 0.05, for second NS equals p less than 0.1. For total bile acids (TBA) there was no significant difference between groups (1) and (2). Women with fibrocystic disease did not seem to have high fecal steroids when compared to women with other types of benign breast lesions. Variations in degree of obesity between the three groups could not account for the observed differences as these persisted even among the subgroups of lean women. The findings support the concept of a common etiologic mechanism between benign and malignant breast lesions which seems to be linked to increased cholesterol synthesis and degradation in these two entities. (no Refs)

8. HORMONAL PATTERN AND SEX HORMONE BINDING GLOBULIN IN PLASMA OF WOMEN WITH CYSTIC BREAST DISEASE (MEETING ABSTRACT).

Berta L, Frairia R, Bumma C, Navello C, Mossetti C, Rovero E, Gaidano G
Patologia Speciale Medica B and Clinica Medica B, Univesita di Torino, Torino, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A25 1981

Fibrocystic mastopathy is a benign disease of fertile women, considered as a clinical condition at high risk for breast cancer. Etiopathogenesis is still uncertain but often the clinical onset has been related to plasma sex hormone imbalance. Sex Hormone Binding Globulin (SHBG) could be also involved. Recently SHBG has been hypothized to play a significant role in breast cancer development. The aim of present work was to study plasma hormonal pattern (E1; E2; P; prolactin, PRL) with respect to Sex Hormone Binding Globulin binding capacity (SHBG-bc) in fertile women with fibrocystic breast disease. In plasma of 57 women with fibrocystic breast disease (aged 18-42 yr) and of 30 normal control women (aged 21-45 yr) the following parameters have been evaluated: E1, E2, P, PRL by radioimmunoassay (RIA) (Biodata); SHBG-bc by an equilibrium partition technique (PEG/Dextran). All subjects were studied in the luteal phase of the menstrual cycle: they had body wt in normal range and were free from endocrinological, hepatic or renal diseases. Progesterone plasma levels significantly lower in patients than in controls are according to the data observed by Mauvais-Jarvis et al and confirm the hypothesis that altered ratio Estrogens/Progesterone interferes in the onset of the disease. Estradiol-17-beat and estrone plasma levels in our cases do not show significant difference, but SHBG-bc is lower in the patients than in normal subjects. These data support that Progesterone and SHBG-bc deficiency respectively induce a relative increase of estrogen plasma levels, influencing mammary epithelium proliferation. (no Refs)

9. BREAST CANCER: A COMPARISON OF RESPONSE TO ENDOCRINE THERAPY AND OESTROGEN EXCRETION PATTERNS INCLUDING UNUSUAL METABOLITES.

Castagnetta L, D'Agostino G, Lo Casto M, Traina A, Leake RE
Cancer Hosp. Centre 'Maurizio Ascoli', 90127 Palermo, Italy
Br J Cancer; 44(5):670-674 1981

The urinary excretion patterns of estrogen metabolites, including unusual metabolites, were determined by gas chromatography and mass spectrometry for 63 women with advanced breast cancer and 39 normal postmenopausal women. The concentration of total unusual metabolites excreted was found to be an excellent discriminant between breast-cancer patients and controls (p less than 0.0001). Discrimination between responders and non-responders to endocrine therapy was attempted, using several different indices. Of these, the ratio of Classical Estrogens to Unusual Metabolites (CE/UM) proved a fair discriminant, but the product of this ratio and the estriol ratio (CE/UM x E3R) was much the best discriminant. This product, termed a Pattern Index, has considerable potential, not only as a discriminant for selecting therapy, but also as a rapid index of patient response to that therapy. (Author abstract) (23 Refs)

10. SERUM CONCENTRATIONS OF TOTAL AND NON-PROTEIN-BOUND OESTRADIOL IN PATIENTS WITH BREAST CANCER AND IN NORMAL CONTROLS.

Moore JW, Clark GM, Bulbrook RD, Hayward JL, Murai JT, Hammond GL, Siiteri PK
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Int J Cancer; 29(1):17-21 1982

In premenopausal women with breast cancer, total serum estradiol (E2) concentrations are normal, but nonprotein-bound E2 concentrations are significantly raised. This is not due to low sex-hormone-binding-globulin (SHBG) binding capacities, which are within the normal range, and is unlikely to be due to the small but significant decrease in albumin concentrations. In post-menopausal patients, both total and non-protein-bound E2 are significantly raised; this may be explained partially by lower SHBG binding capacities. In patients and controls there is a highly significant correlation between non-protein-bound E2 and SHBG, but for a given SHBG binding capacity, the patients have more non-bound E2 than controls. It is concluded that the breast in women with breast cancer may be exposed to elevated levels of biologically active E2, although the reasons for this remain obscure. (Author abstract) (19 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

11. MAINTENANCE OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER.

Ben-David M, Dror Y, Biran S
Dept. Pharmacology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91010 Jerusalem, Israel
Isr J Med Sci; 17(9/10):965-969 1981

Breast tissue specimens of 110 women with various stages of breast cancer were tested in vitro to determine their specific binding sites for human prolactin. In contrast to the case of steroid receptors, binding sites for prolactin were found in the vast majority of breast cancer tissue. Distribution profiles giving amount of prolactin receptor and their affinity coefficients were found to be similar in the tissues of women whose ages, hormonal status, or stage of breast cancer varied. These findings show that in contrast to steroid receptors, human breast cancer tissue maintains binding sites for prolactin. The findings also indicate that there may be a higher dependency of breast cancer on prolactin than on steroids. Clinical trials must be carried out to determine the role of 'positive' prolactin receptors in prognosis and prediction of response to future hormone therapy. (Author abstract) (20 Refs)

12. MEASUREMENT OF ESTRADIOL RECEPTORS IN PRIMARY AND METASTATIC BREAST CANCER.

Antunes JR
Laboratorio de Radioensaio, Laborens S/C Ltda., Rua Itacolomi, 601, cj 14, CEP 01239, Sao Paulo, Brazil
Rev Paul Med; 97(7/9):103-105 1981

Of 61 patients (34-78 yr old) with mammary carcinoma (MC) 58 had primary and 3 metastatic MC (one each: pleura, axillary lymph node, and peritoneal ascitic liquid). Twenty seven percentage of the patients were before menopause and after menopause were 73%. Primary MC in the right were 55% and in the left breast 45%. Tumor wt was 0.3-3.4 g, they were frozen immediately and used for determination of estrogen receptors (ER). Of 61 patients, 47 had ER above 3 femtomoles (fm)/mg protein, 12 patients had 3-10 fm/mg, 28 patients had 10-100 fm/mg, 6 patients had 100-1,000 fm/mg, and in 1 case ER was greater than 1,000 fm/mg protein. Only 14 patients had ER of less than 3fm/mg protein. The three patients with metastatic MC had ER of 6, 6.3, and 86.1 fm/mg protein. The ER majority (50-70%) were located in the cytosol. (12 Refs) (In POR)

13. BIOCHEMICAL MARKERS AS INDICATORS OF PROGNOSIS IN ACUTE NONLYMPHOCYTIC LEUKEMIA (ANLL).

Skoog L, Nordenskjold B, Ost A, Andersson B, Hast R, Giannoulis N, Reitzenstein P
Dept. Pathology, Karolinska Hosp., Stockholm, Sweden
Adv Enzyme Regul; 19:287-293 1981

Twenty-five cases of ANLL were analyzed with respect to content of TdT, glucocorticoid receptor, adenosine deaminase and 5'-nucleotidase. We found that high levels of either TdT or the glucocorticoid receptor were positively correlated to both remission frequency and survival time. Thus, these two biochemical parameters contribute new valuable prognostic information in ANLL. We were unable to identify 5'-nucleotidase and adenosine deaminase as prognostic indicators in ANLL. (Author abstract) (10 Refs)

14. MEASUREMENTS OF DNA SYNTHESIS AND ESTROGEN RECEPTOR IN NEEDLE ASPIRATES AS POWERFUL METHODS IN THE MANAGEMENT OF MAMMARY CARCINOMA.

Nordenskjold B, Skoog L, Wallgren A, Silfversward C, Gustafsson S, Ljung BM, Westerberg H, Gustafsson JA, Wrange O
Karolinska Hosp., Karolinska Inst. and Univ. Linkoping, Linkoping, Sweden
Adv Enzyme Regul; 19:489-496 1981

Techniques used in management of mammary carcinoma (MC) are presented. Monitoring biochemical parameters in small tissue samples from needle aspirates is of value. Measurement of estradiol receptor (ER) in MC is based on the electrofocusing of 3H-estradiol bound receptor in slices of polyacrylamide gel. ER level in the tumor correlates with pathological type of MC. Medullary carcinoma and comedocarcinomas are receptor poor; papillary carcinomas are receptor rich. Measurements of ER and DNA in needle aspirates from primary or recurrent carcinoma correlate significantly. Primary MC from 50 patients were characterized by 3H-thymidine incorporation and ER analysis of needle aspirates. Results correlating with pathological analysis showed that ductal carcinomas of a low degree of differentiation have a decreased mean receptor value. Decreased DNA synthesis can be registered 1-3 wk after initiation of endocrine therapy, before a significant reduction in tumor diameters can be noted. (13 Refs)

15. AFFINITY CYTOCHEMISTRY VISUALIZES SPECIFIC ESTROGEN BINDING SITES ON THE PLASMA MEMBRANE OF BREAST CANCER CELLS.

Nenci I, Marchetti E, Marzola A, Fabris G
Istituto di Anatomia e Istologia Patologica, Univ. Ferrara, 44100 Ferrara, Italy
J Steroid Biochem; 14(11):1139-1146 1981

A cytochemical technique involving estradiol labeled covalently with macromolecular fluorescent probes was used to detect possible estrogen-binding sites on the plasma membrane of viable human breast cancer cells. At 4 C, breast cancer cells, but not other non-epithelial cell types, showed bright fluorescence diffusely distributed over the cell surface and in a ring pattern. Binding occurred by a saturable pathway, because pretreatment of cells with the same ligand in 'cold' form abolished labeling. Non-estrogen steroid hormones; synthetic estrogen, and anti-estrogen did not hinder binding, indicating that binding is structurally specific for natural estrogen. Binding sites showed temperature-sensitive lateral mobility in the plane of the membrane, which led to formation of small clusters, patches, and polar caps at 23 or 37 C. Results indicate that estrogen-target cells have plasmalemmal estrogen-binding sites, which do not involve classical cytoplasmic receptors. Translational mobility of binding sites is consistent with their potential receptor nature. (40 Refs)

16. QUANTITATIVE OESTRADIOL RECEPTOR VALUES IN PRIMARY BREAST CANCER AND RESPONSE OF METASTASES TO ENDOCRINE THERAPY.

Campbell FC, Blamey RW, Elston CW, Morris AH, Nicholson RI, Griffiths K, Haybittle JL
(c/o Blamey), City Hospital, Nottingham, England
Lancet; 2(8259):1317-1319 1981

The relationship between estrogen receptor (ER) status of primary breast cancer and response of the secondary cancer to endocrine therapy, and the relationship between response and measured receptor values in the primary tumor were investigated. Six hundred and twenty primary breast cancer patients with tumors less than 5 cm in diameter and no evidence of distant metastasis were treated with simple or sc mastectomy. Endocrine therapy (oophorectomy for premenopausal patients and 20 mg tamoxifen bid for postmenopausal patients) was subsequently administered to 106 patients with evidence of metastasis. Of 95 assessable patients, 19 responded to treatment; 17 of these had ER positive and 2 had ER negative cancer. Median duration of remission was 26 mo for patients with ER receptor-high cancer (greater than 50 femtomole/mg cytosol) and 12.2 mo for those with receptor-low cancer (less than 50 femtomole/mg cytosol). Metastatic tumor biopsy in 24 patients showed unchanged ER status in 18; 3 who had had ER positive primaries developed ER negative secondaries and 3 who had had ER negative primaries had measurable amounts in the secondary tumor. Likelihood and possibly duration of remission of subsequent metastasis after endocrine therapy may be predicted on the basis of the ER value in the primary malignancy at the time of mastectomy. (8 Refs)

17. THE EFFECTS OF GLUCOCORTICOID THERAPY ON GLUCOCORTICOID RECEPTORS IN LEUKEMIA AND LYMPHOMA.

Shipman GF, Bloomfield CD, Smith KA, Peterson BA, Munck A
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Blood; 58(6):1198-1202 1981

Measurement of glucocorticoid receptors appears to be useful for selecting which patients with leukemia and lymphoma should receive glucocorticoid therapy. To determine the effect of recent or concurrent glucocorticoid therapy on the number of measured tumor glucocorticoid receptor sites, 18 patients with leukemia and lymphoma were studied. Baseline determinations of numbers of glucocorticoid receptors were performed on the malignant cells circulating in the patients' peripheral blood. Glucocorticoid therapy was then instituted consisting of dexamethasone 4 mg po every 6 hr. Repeat determinations of the number of glucocorticoid receptor sites were performed within 24 hr and at various subsequent times from the start of therapy. When compared to baseline receptor numbers, 16 of the 18 patients demonstrated a decrease in receptor number (median decrease 1,651 sites/cell) after the start of glucocorticoid therapy. The magnitude of the change in receptor number was independent of the initial number of receptors. Our results suggest that in order to accurately interpret glucocorticoid receptor numbers in patients with leukemia and lymphoma, glucocorticoid should not be administered for 3 wk prior to determinations of receptor levels. (Author abstract) (11 Refs)

18. HORMONAL RECEPTORS AND RESPONSE TO TREATMENT OF BREAST CANCER: A RETROSPECTIVE EVALUATION IN 60 PATIENTS.

Loven D, Rakowsky E, Stein JA, Geier A, Lunenfeld B
Inst. Oncology, Beilinson Medical Center, 49100 Petah Tikva, Israel
Isr J Med Sci; 17(9/10):960-964 1981

Response to several types of endocrine therapy or chemotherapy was evaluated in 60 patients with breast cancer. Estrogen and progesterone receptors were determined by radioimmunoassay. Response to endocrine therapy was significantly higher (p less than 0.01) among estrogen receptor (ER)-positive cases than among ER-negative cases. The response to chemotherapy did not differ significantly between the two groups. The results of this small series support the conclusion that determination of ER is valuable in planning endocrine treatment of the breast cancer patient, whereas response to chemotherapy does not correlate with ER levels. (Author abstract) (15 Refs)

19. CLINICAL STUDY OF ESTROGEN RECEPTOR IN CHINESE PATIENTS WITH BREAST CANCER.

Liu TJ, Chi CW, Cheng EC, Chyr R, Lee C, P'Eng FK
Div. General Surgery, Dept. Surgery, Veterans General Hosp., Taipei, Republic of China (Taiwan)
Taiwan I Hsueh Hui Tsa Chih; 80(9):909-918 1981

Preliminary studies of the correlation between tumor estrogen receptor (ER) contents and clinical response to endocrine manipulation of 126 recurrent or metastatic breast cancer patients and use of primary cancer specimens to predict hormone dependency of potential metastases are described. Positive ER levels were found in 16/43 Stage I specimens, 11/37 Stage II, 12/16 Stage II, and 7/10 Stage IV. Of the 106 primary and 20 secondary cancer patients, 46 and 5, respectively, were ER+. In the secondary cancer group, 4/16 locally recurrent or chest wall specimens, 1/2 lung and pleural cavity specimens, and 0/2 of cervical lymph nodes from patients with advanced metastatic breast cancer were ER positive. The mean of positive ER was higher in the postmenopausal group (62.85 +-13.91 vs 38.28 +-8.12 femtomole/mg cytosol pro tein). The same pattern was found in negative ER cases (2.77 +-0.50 vs 1.86 +-0.52 femtomole/mg cytosol protein). Both male breast cancer specimens were ER+. Of 30 benign breast cancer specimens examined, 6 were ER+. Hormonal treatment of 26 patients produced a fairly high response rate in ER+ patients. Ablative therapy was performed in 12 patients (6 ER+ and 6 ER-). All 5/5 ER+ and 0/5 ER- patients responded to oophorectomy. Neither ER+ nor ER- patients responded to bilateral adrenalectomy. Tamoxifen treatment produced responses in 3/5 ER+ and 0/2 ER- patients. Combined therapy with oophorectomy and tamoxifen also produced a good response in two ER+ patients. One ER+ and 1/2 ER- patients responded to oophorectomy and testosterone treatment. Therapy complications are described. Results indicated that the cytoplasmic ER assay in breast cancer patients is a reliable indicator for selection of good responders to hormonal treatment. (25 Refs)

20. STEROID HORMONE RECEPTORS AND PROSTAGLANDIN SYNTHESIS IN BENIGN BREAST DISEASES (MEETING ABSTRACT).

Rolland PH, Serment H, Martin PM
Laboratoire de Cancerologie Experimentale-Faculte Nord de Medecine, Clinique de Gynecologie-Obstetrique Hopital de la Conception, Marseille, France
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A8 1981

Studies on steroid receptor (SR) and prostaglandin (PG) synthesis in benign breast disease, from our viewpoint, are involved in further characterizing mechanisms of hormone cancerogenesis and tissular-hormone dependence of breast cancer in humans. Particularly, we have previously presented evidence suggesting that an elevated PG production is a marker of high metastatic potential for neoplastic mammary cells due to the improvement of the cellular autonomy which is concomitant to the loss of tissular-hormone dependence for these cells. When measured in both phases of the menstrual cycle of women suffering from benign mastopathies, plasma levels of both estradiol (E2) and progesterone (P) were lower in patients than in control women, resulting in an hormone imbalance with a relative excess of estrogen whose magnitude varies according to the individual degree of deficiency of P and E2. In both phases of the cycle, PGE blood levels were significantly higher in patients with benign mastopathies than in normal women. At the lesion's level, PG production was observed to be higher in benign disease than in normal breast. An estrogen-directed synthesis of PG is proposed to occur concomitantly to the benign epithelial hyperplasia induced by hormone imbalance. Similar results concerning estrogenic regulation of PG synthesis was observed in breast cancer. Both estrogen receptor (ER) presence and content increase as epithelial cell hyperplasia does in benign breast disease. A significant level of ER-PR couple appears in the lesions exhibiting lobular and ductal hyperplasia. Moreover, each lesion of high-intensity hyperplasia, ie diffuse ductal and lobular cell proliferation and hyperplasia associated or not with multiple papilomas, was found to be ER-PR positive while ER-PR couple was not detected in lesions in which fibrocystic alterations were associated with fibrosing adenosis. (no Refs)

21. PROGESTERONE INSUFFICIENCY IN BENIGN BREAST DISEASE (MEETING ABSTRACT).

Kuttenn F, Fournier S, Sitruk-Ware R, Martin PM, Mauvais-Jarvis P
Service d'Endocrinologie, Hopital Necker, Paris, France
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy Italian Society of Endocrinology; :A10 1981

That the different clinical expressions of benign breast disease are due to an ovarian dysfunction. Evidence for this was found in an investigation of 184 patients with various benign breast diseases (permanent mastodynia, fibroadenomas, cystic mastitis and fibrocystic disease). In all these patients the luteal plasma progesterone to estradiol ratio was found to be significantly lower than in normal women. In vitro: estradiol and progesterone receptors were found in fibroadenomas with high epithelial cell density and no fibrosis. In the case of old lesions with low cell density and extensive fibrosis, no receptors were found. Cytosolic and nuclear estradiol and progesterone receptors were also studied in fibroadenomas of high cellular density according to the phase of the menstrual cycle. Cyclic changes in level and distribution of these receptors were similar to those noted in the human endometrium: the highest levels were found in the late follicular phase, whereas both estradiol and progesterone receptors decreased in the luteal phase. Moreover, the correction of luteal insufficiency by progestagen treatment induces a translocation of the progesterone receptor from the cytosol to the nucleus, which warrants the efficiency of such a treatment. (no Refs)

22. HISTOCHEMICAL DEMONSTRATION OF ESTROGEN RECEPTORS IN BREAST CANCER.

Paulsen SM, Johansen P, Rasmussen KS, Mygind H
Patologisk institut, Aalborg sygehus Nord, DK-9000 Aalborg, Denmark
Ugeskr Laeger; 143(47):3119-3123 1981

Histochemical method for the detection of estrogen receptors (ERs) in breast carcinoma tissue is described, and results obtained by this method in tissue specimens from 46 breast cancer patients are reported. The histochemical detection of ERs is based on counting of fluorescent (positive) cells after incubation with fluorescein isothiocyanate-conjugated 17-beta-estradiol. ER+ carcinomas were defined as those containing more than 10% fluorescent cells, which was found consistent with the biochemical criterion of ER+ breast carcinoma (greater than 10 femtomoles/mg protein). The patients included 14 premenopausal and climacteric patients (Group I) and 32 patients in the menopause (Group II). The frequencies of ER+ carcinomas were 8/14 in Group I and 24/32 in Group II. The frequencies of ER+ carcinomas were 25/38 for infiltrating ductal carcinomas, 6/7 for infiltrating lobular carcinomas, and 1/1 for colloid carcinoma. Even though the relationship between the histochemically and biochemically demonstrated ERs is not fully elucidated, the histochemical method is able to supplement the biochemical method. (15 Refs) (In DAN)

23. HORMONE RECEPTORS AND BREAST CANCER.

Howanitz JH
Div. Clinical Pathology, Dept. Pathology, State Univ. of New York, Upstate Medical Center, 750 East Adams St., Syracuse, NY, 13210
Hum Pathol; 12(12):1057-1059 1981

Prognostic value of measurement of cytoplasmic estrogen receptors (ER) in breast cancer patients (BC) is discussed. ER analysis was shown to improve the response rate from 30% in unselected patients to 55% in ER positive BC patients. The presence of ER in a biopsy specimen was found to correlate with the positive response to the decrease of estrogen level, although the ER assay did not always predict the response to endocrine therapy. The discrepancies in the results of ER assay and the response to the endocrine therapy can be explained by improper specimen handling, wrong classification of ER status, or qualitative changes in ER status during tumor progression. Measurements of unoccupied nuclear ER may be useful in identifying the group of BC patients who can benefit from antiestrogens. Measurements of progesterone receptors can be used as an indicator of functioning ER. In addition to steroid hormone receptors, prolactin or growth hormone receptors might be useful in predicting the response to hormone therapy. (5 Refs)

24. UNOCCUPIED BINDING SITES FOR OESTROGEN IN NUCLEI OF A BREAST TUMOR CELL LINE (MCF-7).

Geier A, Haimsohn M, Malik Z, Lunenfeld B
Inst. Endocrinology, Chaim Sheba Medical Center, Tel Hashomer, Israel
Biochem J; 200(3):515-520 1981

A method to measure both occupied and unoccupied estrogen receptors directly in the crude nuclear fraction of the MCF-7 cells was developed. The receptors had high affinity for estradiol (Kd approx 0.7 nm) and binding specificity characteristics of estrogen receptors. A substantial amount of the unoccupied receptors were found in the crude nuclear fraction. Several experiments excluded the possibility that the unoccupied nuclear receptor might be a cytoplasmic contaminant. Multiple extractions with Tris buffer released about 75% of the total receptor content, leaving the rest unextractable in the crude nuclear fraction. Nuclei purified by centrifugation through 1.8 M-sucrose and treatment with 0.7% Triton X-100, or by centrifugation through 50% glycerol with 0.1% Triton X-100 contained similar amounts of unoccupied receptors to that found in the crude nuclear fraction. In cells cultured during 5 days after preconfluency a three-fold increase in the amount of unoccupied cytoplasmic receptors occurred, whereas the amount of unoccupied nuclear receptors did not change significantly and conversely in cells exposed to increasing concentrations of estradiol the unoccupied cytoplasmic receptor was continuously depleted but no considerable change in the unoccupied nuclear receptor was found. (Author abstract) (23 Refs)

25. INFLUENCE OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON ESTROGEN AND PROGESTIN BINDING PROTEINS IN UTERI AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS OF THE RAT.

Heidemann PH, Wittliff JL, Calhoon RE, Boylan ES
(c/o Wittliff) Dept. Biochemistry, Health Sciences Center, Louisville, KY, 40292
J Toxicol Environ Health; 8(4):667-686 1981

Various characteristics of steroid binding proteins from mammary tumors and from uteri of rats exposed prenatally to diethylstilbestrol (DES) were examined. Pregnant rats were treated with no hormone (group A) or with a total dose of 1.2 ug DES during the second (group B) or third (group C) trimester of gestation. Female offspring received 7,12-dimethylbenz(a)anthracene (DMBA) at day 50 +-1. Animals with large mammary tumors were subjected to bilateral ovariectomy. The experiment was terminated 7 mo after carcinogen treatment. High-affinity binding sites for (3H)estradiol-17beta and (3H)R5020 were found in all mammary tumors assayed. Estrogen receptor forms 8S and 4S were identified on sucrose gradients of low ionic strength regardless of prenatal treatment. Progestin receptors (PR) sedimenting at 4S were also identified in the tumors. PR form 7-8S was found only in tumors from intact animals. PR levels diminished after ovariectomy in mammary tumors and in uteri. Uterine progestin binding capacities and uterine wet wt did not decrease proportionally after ovariectomy in group C. PR capacities in mammary tumors from group C were higher than in other groups. Cytosol from mammary tumors in group C intact rats also had elevated PR levels. Uterine estrogen binding capacities did not vary significantly. Prenatal exposure to DES during the third trimester appeared related to persistent biochemical alterations in rat mammary tumors and uteri. Earlier exposure did not have the same effect. (61 Refs)

26. FLUORESCEINATED ESTRONE BINDING BY HUMAN AND MOUSE BREAST CANCER CELLS.

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Cancer Res; 42(2):540-549 1982

A proportion of single, intact, viable cells derived from mouse and human breast cancers, when incubated with 17-fluoresceinated estrone, displayed fluorescence in all instances. The percent age of cells which were marker positive in mouse mammary tumors was remarkably uniform (approx 35%), whereas in human breast cancers, it varied considerably (3 to 58%). While fluorescence of the entire cell most commonly occurred, staining of either the nucleus or the cytoplasm was observed frequently. Mouse uterus and liver were also marker positive. The proportion of such cells decreased in incidence following in vitro incubation with estradiol and tamoxifen or following administration of tamoxifen prior to tissue removal, findings indicative of 17-fluoresceinated estrone binding to estrogen receptor (ER). Experience with the cytochemical method as used in the present studies leads us to conclude that this is a technique which may by readily and rapidly carried out and is one which deserves more widespread evaluation. Since standard biochemical methods determine total ER in tumor cytosol and since cytochemical techniques measure the proportion of cells containing ER, the two are complimentary. When used simultaneously, they may provide more definitive information than is obtainable from either alone. (14 Refs)

27. SECRETION-ASSOCIATED LECTIN-BINDING SITES AS A PARAMETER OF HORMONE DEPENDENCE IN MAMMARY CARCINOMA.

Klein PJ, Vierbuchen M, Wurz H, Schulz KD, Newman RA

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Br J Cancer; 44(5):746-748 1981

Hormone dependency in mammary carcinoma was studied with the aid of lectins from peanut (PNA: peanut agglutinin) and Helix pomatia (HP), which have high affinities for D-galactosyl-(1-3)-N-acetyl-D-galactosamine and N-acetyl-D-galactosamine, respectively. Experiments were performed on formaldehyde-fixed tissue sections from 75 patients. After treatment of tissue sections with neuraminidase to expose any sialic acid-covered receptors, PNA binding was seen within cytoplasmic vacuoles of breast tissue with secretory malfunction; in well-differentiated carcinomas, binding to apical surfaces and on secretions lying within the glandular structures was observed. Of 46 specimens of mammary tumors, 68% had PNA receptors as well as estrogen (E) and progesterone (P) receptors. Only 45% had PNA receptors when only E receptors were detected. Only 23% of specimens with no detectable E or P receptors had PNA receptors. Greater PNA binding occurred in the primary tumors than in axillary-lymph node metastases. Responsiveness of 29 breast cancer patients to endocrine therapy was determined. Of lectin- (PNA and HP) positive patients, 82% showed a response to hormone therapy. Only 24% of the lectin-negative group showed similar responses. A poor correlation was found between lectin-receptor expression and response to chemotherapy. Results indicated that the lectin-binding method is a useful hormone-receptor assay. (7 Refs)

28. PURIFICATION AND PARTIAL CHARACTERIZATION OF A 17BETA-ESTRADIOL-BINDING MACROMOLECULE IN THE HUMAN PANCREAS.

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Dept. Medical Nutrition and Clinical Chemistry, Karolinska Institutet, Stockholm, Sweden

Cancer Res; 42(2):633-737 1982

Studies have been performed in order to investigate the presence of estrogen-binding proteins in the human pancreas that may provide the biochemical basis for tissue-specific treatment of pancreatic carcinoma with estrogen-based cytotoxic drugs. Using in vitro techniques, an estrogen-binding macromolecule has been purified from human pancreatic cytosol. With estradiol as ligand, Kd was calculated to be 1.7 x 10(-7) M, and this protein was found to constitute about 4% of the total protein content in the cytosol. No metabolism of estradiol was detected under the in vitro conditions used. Competition experiments indicated that, besides estradiol, the protein also had some affinity for estrone and estriol but not for testosterone, progesterone, or dexamethasone. The protein was purified to homogeneity using chromatography on concanavalin A and hydroxylapatite followed by preparative polyacrylamide gel electrophoresis. The purified protein, still able to bind [3H]estradiol, gave one single protein-staining band when analyzed using different electrophoretic systems. The steroid:protein complex did not bind to phosphocellulose or DNA-cellulose and did not show any similarities to steroid receptor proteins. The complex has a Stokes' radius of 52 A and a sedimentation coefficient of 3S. The biological significance of the macromolecule is unknown, but the protein is probably synthesized in the pancreas since no similar protein could be detected in serum. Studies are now being carried out to investigate whether this novel protein in the human pancreas may interact with complexes between cytotoxic agents and estrogens and provide the basis for tissue-specific treatment of pancreatic carcinoma. (Author abstract) (18 Refs)

29. STEROID RECEPTORS IN A GROUP OF BRAZILIAN BREAST CANCER PATIENTS.

Brentani MM, Nagai MA, Fujiyama CT, Goes JC

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J Surg Oncol; 18(4):431-439 1981

Two hundred and forty-two primary breast cancers were assayed for estrogen receptors (ER). Of these, 202 were analyzed for progesterone receptors (PR) and 155 for glucocorticoid receptors (GR). ER was positive in 58% of the specimens; PR and GR were positive in 57%. A positive association was found between ER but not PR or GR frequency and age. Frequency of ER, PR, and GR positivity was approx the same in premenopausal and postmenopausal women but ER content was much higher in postmenopausal women. About 70% of ER+ patients were also PR+ and GR+. Both frequency of PR positivity as well as av concentration, and frequency of GR positivity as well as av concentration were positively correlated with ER. (Author abstract) (30 Refs)

30. THE PRESENCE OF A SECOND, SPECIFIC ESTROGEN BINDING SITE IN HUMAN BREAST CANCER.

Panko WB, Watson CS, Clark JH
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 14(12):1311-1316 1981

Type II estrogen binding site (II EBS) was analyzed in human breast tumor specimens. Saturation analysis of cytosol derived from pooled tumor specimens was conducted over the 3H-estradiol (3H-ES) concentration range 0.5-120 nanoM (nM). Scatchard plotting of saturation data revealed the presence of a two-component binding system. The type I site, believed to be cytoplasmic estrogen receptor (ER), displayed an affinity and concentration compatible with the ER system. The type II site had a markedly lower affinity for 3H-ES and significantly higher concentration. A similar two-component Scatchard plot was obtained when moxestrol was used with a different pool of tumor tissue. The post-labeled sucrose gradient method was used with cytosol derived from pooled tumor tissue. If cytosol was pre-labeled with 40 nM 3H-ES, the specific binding at both the 8S and 4S regions of the gradient showed some augmentation. However, if the cytosol was post-labeled, marked augmentation of specific binding in the 4S region of the gradient occurred. Tumors of the colon (2), lung (2), and muscle (1) were subjected to pre- and post-labeled sucrose gradient analysis with 40 nM 3H-ES. The difference between specific binding in the 4S region of the pre-labeled (2 nM) and the post-labeled (40 nM) gradient was defined as the amount of type II EBS in the tumor. Neither ER nor type II EBS were detected in any of the five tumors. When the concentration of type II EBS was correlated with the concentration of ER, a very strong positive correlation was noted. The results indicated that breast cancer cytosol contains a specific, secondary estrogen binding site. (16 Refs)

31. HORMONE RECEPTOR ANALYSIS AND TESTING FOR SENSITIVITY TO CYTOSTATIC DRUGS: VALUE IN PLANNING OF ADJUVANT THERAPY FOR MAMMARY CARCINOMA.

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Dtsch Med Wochenschr; 106(51/52):1749-1754 1981

The significance of tests for hormone receptors and sensitivity to cytostatic drugs (CS) in planning therapy for mammary carcinoma (MC) is reviewed. Assays of tumor tissue extracts (cytosols) by hormone-binding methods such as the charcoal absorption technique allow detection of tumor cell receptors for estradiol (ED), progesterone (PG), androgen, and prolactin, of which the first two have principal clinical significance. ED receptors (EDR) are found in 60-85% of MC; PG receptors (PGR) are found in approx half of MC. Hormonal therapy produces a response of 50-60% in MC with EDR and 83% in MC with both EDR and PGR. EDR and PGR status determinations therefore are important in determining treatment. CS tests include in vivo transplantation in mice and in vitro incubation with cytostatic drugs. A disadvantage of in vitro tests is related to possible cell selection and other factors, not accurately reflecting the actual behavior of the tumor in the patient. In one series of cases only approx 30% of MC could be successfully worked up and evaluated. The value of CS testing, in contrast to the established value of EDR and PGR testing, is uncertain in planning of adjuvant therapy. (52 Refs) (In GER)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

32. HORMONE RECEPTORS IN BREAST CANCER.

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Minn Med; 64(12):761-763 1981

Standardization, quality control, and results of the hormone receptor assay are discussed. Primary breast cancer specimens were assayed for estrogen (ER), and/or progesterone (PR) hormone receptors. A total of 632/987 (64%) tumors tested were positive. The menopausal state was identified in 374/632 patients. Histologic description of 229 specimens was: 190 ductal carcinoma, 22 comedocarcinomas, 12 medullary carcinomas, 5 lobular carcinomas, 2 adenocarcinomas. Results obtained disclosed ER positive receptor in 85/145 (58.5%) premenopausal and 147/204 (67.5%) in postmenopausal patients. PR receptors are determined only if ER is positive. For both ER and PR receptors in 180 premenopausal patients were studied showing 133 (73.8%) with both positive receptors. Positive receptors were found in 90/123 (74%) postmenopausal patients. The hormone receptor determinations in breast cancer are important in prognosis and management. Meticulous control of sample storage, handling, periodic double testing of materials, and sample assays are important. (9 Refs)

33. SPECIFIC ESTRADIOL BINDING IN SCHWANNOMAS, MENINGIOMAS, AND NEUROFIBROMAS.

Martuza RL, MacLaughlin DT, Ojemann RG, Salcman M
Massachusetts General Hosp., Boston, MA, 02114
Neurosurgery; 9(6):665-671 1981

Specific estrogen receptors (ER) were found in the cytoplasmic fractions of 7/16 schwannomas (acoustic neurinomas), 7/10 meningiomas, and 1/6 neurofibromas using tritiated estradiol and R5020. In the unselected series of 32 patients, 11 were men, and 21 were women, with mean ages of 46.6 and 47.8 yr, respectively. Overall incidence of ER was 15/32, with 5/11 (45%) in males and 10/21 (48%) in females. While the concentration of estradiol binding sites, estimated by saturation binding analys is, covered a wide range (21-2,430 femtomoles/g), overall, meningiomas contained the highest amount. Progestin binding, measured in five patients, was detected in two meningiomas (both females), while another meningioma and two neurofibromas, showed none. The possible role of estradiol in the pathogenesis or modulation of meningeal and Schwann cell tumors, as well as in the genetic disorder of neurofibromatosis, is discussed. (35 Refs)

34. OVARIAN CARCINOMA: HISTOLOGIC AND CLINICAL CORRELATION OF CYTOPLASMIC ESTROGEN AND PROGESTERONE BINDING.

Creasman WT, Sasso RA, Weed JC, McCarty KS
Div. Oncology, Duke Univ. Medical Center, Durham, NC, 27710
Gynecol Oncol; 12(3):319-327 1981

Primary ovarian carcinomas from 18 patients, ages 27-79, were evaluated for the presence of estrogen- and progesterone-binding proteins. The levels of cytosolic sex steroid receptor were compared to histology, nuclear grade, and the patients' clinical course. The data suggest that nuclear grade and receptor status each correlate with the patients' clinical course. The simultaneous presence of both estrogen and progesterone receptor proteins tend to be noted in tumors with more well-differentiated nuclei. It is suggested that the determination of biochemical cytosolic receptor status may become an important addition to tumor type, nuclear grade, and staging as prognostic indicators in patients with ovarian carcinoma. Histochemical staining for estrogen-binding localization did not correlate with SDGA and DCCA receptor analysis nor with clinical parameters. (Author abstract) (31 Refs)

35. STRUCTURE, STABILITY, METHYLATION, EXPRESSION AND GLUCOCORTICOID INDUCTION OF ENDOGENOUS AND TRANSFECTED PROVIRAL GENES OF MOUSE MAMMARY TUMOR VIRUS IN MOUSE FIBROBLASTS.

Hynes NE, Rahmsdorf U, Kennedy N, Fabiani L, Michalides R, Nusse R, Groner B
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Gene; 15(4):307-317 1981

A sequence of mouse genomic DNA containing an endogenous mouse mammary tumor virus (MMTV) provirus, which was isolated by molecular cloning in lambda vector phage, has been reintroduced into cultured mouse L cells, using the thymidine-kinase (TK) cotransfection technique. Transfection of mouse cells with a lambda-MMTV recombinant DNA molecule, MMTV RNA expressed in the GR-40-transfected L cells, stability of transfected MMTV DNA in LTK+GR-40+ cells, hypomethylation of MMTV-transfected DNA, and MMTV-specific proteins in LTK+GR-40+-tranfected cells are discussed. Individual cell clones that acquired the transfected MMTV proviral DNA have been isolated. The transfected DNA remains stable in these cells and does not become methylated. It is transcribed into MMTV RNA, and the transcription is stimulated by glucocortic oid hormones. Results suggested that the transfected TK DNA and the MMTV proviral DNA are linked. Clone GR-40 contains a region of DNA which mediates the response to glucocorticoid. (39 Refs)

36. MORPHOLOGICAL CHANGES INVOLVED IN HORMONAL TRANSFORMATION OF ENDOMETRIAL ADENOACANTHOMA DURING PROGESTIN THERAPY.

Shendereva TS, Shvedova LA
Moldavian Res. Inst. Oncology, Kishinev, USSR
Vopr Onkol; 27(10):52-56 1981

Changes in the histological structure of endometrial adenoacanthoma, as a result of treatment with 17alpha-hydroxyprogesterone capronate, are discussed. The biopsy and resected material obtained from 11 patients was studied. It was shown that hormonotherapy results in an increased structural and functional differentiation of the glandular and squamous cell components of tumor. Sensitivity to 17alpha-hydroxyprogesterone capronate was established in 81.1% +-11.6 of patients. (Author abstract) (11 Refs) (In RUS)

37. LEUCINE-ARYLAMIDASE ACTIVITY IN UNTREATED AND TREATED BENIGN PROSTATIC HYPERTROPHY AND ADENOCARCINOMATOUS PROSTATE.

Verlooy J, Van Sande M, Van Camp K
Unit. Urology, Universitaire Instelling Antwerpen, Antwerp, Belgium
Acta Urol Belg; 49(4):491-495 1981

Levels of leucine-arylamidase (LAP: leucine aminopeptidase) were determined in 56 prostate tissue specimens, including samples from 42 cases of untreated benign hyperplasia (BHP: 18 middle and 24 lateral lobes), from 6 of treated BHP, and from 8 of prostate adenocarcinoma. The mean LAP value for middle lobes from patients with untreated BHP was 106 U/mg protein (range: 15-303 U/mg protein). For lateral lobes, the mean LAP was 143 U/mg protein (range: 23-362 U/mg protein). The difference between mean LAP values for middle and lateral lobes was statistically significant. Two estrogen-treated BHP patients showed prostate tissue LAP levels of 160 and 242 U/mg protein. Tissues taken from two patients who had undergone regular medroxyprogesterone acetate (MP) treatment showed increased LAP levels (226 and 384 U/mg protein). Two BHP patients who had take MP irregularly exhibited lower prostate LAP activity: 18 and 89 U/mg protein. The mean LAP value for adenocarcinomatous prostates was 27 U/mg protein (range: 19-53 U/mg protein). (6 Refs)

38. EFFECT OF DEXAMETHASONE ON HEXAMETHYLENE BISACETAMIDE-INDUCED FRIEND CELL ERYTHRODIFFERENTIATION.

Osborne HB, Bakke AC, Yu J
(c/o Yu) Dept. Cellular and Developmental Immunology, Res. Inst. Scripps Clinic, La Jolla, CA, 92037
Cancer Res; 42(2):513-518 1982

Friend erythroleukemic cells can be induced to differentiate by chemicals such as dimethyl sulfoxide and hexamethylene bisacetamide (HMBA) in a dose-dependent manner. Others have shown that dexamethasone and other steroid hormones can inhibit the differentiation induced by dimethyl sulfoxide. We show here that dexamethasone has a dual mode of action on the HMBA-induced differentiation of a Friend cell line, DS19. At concentrations above 10(-10) M, dexamethasone inhibits the HMBA-induced differentiation in DS19 cells. We further found that, as the concentration of HMBA is reduced, the amount of dexamethasone required to inhibit differentiation increases. Such inhibition seems to act primarily by decreasing the probability that a cell will become committed to differentiate. Besides, dexamethasone does not inhibit hemoglobin synthesis of cells which are committed in its absence. In addition, we show that sensitivity to the inhibition by dexamethasone is inversely related to the inducibility of of cell populations. The second action of dexamethasone, observed at concentrations between 10(-10) and 10(-13) M, is to increase the proportion of hemoglobin-containing cells relative to that for cells cultured in its absence. The degree of this synergistic effect for induced differentiation is inversely related to the level of induction in the absence of dexamethasone and thus is best observed in the cells cultured at low levels of HMBA. We present evidence that this synergistic effect may be due to an increased viability of the induced cells and possibly an increase in the proliferative capacity of these cells. (Author abstract) (19 Refs)

39. GLUCOCORTICOID REGULATION OF THE HA-MUSV P21 GENE CONFERRED BY SEQUENCES FROM MOUSE MAMMARY TUMOR VIRUS.

Huang AL, Ostrowski MC, Berard D, Hager GL
Lab. Tumor Virus Genetics, NCI, Bethesda, MD, 20205
Cell; 27(2):245-255 1981

Molecular chimeras with the p21 transforming gene of Harvey murine sarcoma virus linked to DNA containing the long terminal repeat (LTR) of mouse mammary tumor virus (MMTV) have been constructed. Transformants of NIH 3T3 cells induced by transfection with MMTV LTR-p21 hybrid DNA have been identified that express the normal p21 gene product. The levels of p21 RNA and protein in these transformants are regulated by physiological concentrations of dexamethasone, a synthetic glucocorticoid hormone. Hybrid transcripts containing p21 gene sequences originate at the normal MMTV viral initiation site. It is concluded that sequences necessary for hormonal control of transcription are completely specified by the viral genome and probably map within the viral LTR. (Author abstract) (45 Refs)

40. MAMMARY TUMOR VIRUS DNA CONTAINS SEQUENCES REQUIRED FOR ITS HORMONE-REGULATED TRANSCRIPTION.

Ucker DS, Ross SR, Yamamoto KR
Dept. Biochemistry and Biophysics, Univ. California, San Francisco, San Francisco, CA, 94143
Cell; 27(2):257-266 1981

Glucocorticoids regulate the rate of transcription of integrated murine mammary tumor virus (MTV) genes in most clones of MTV-infected rat hepatoma tissue culture (HTC) cells. To determin e whether hormonal regulation is mediated from flanking cellular sequences or rather from within the viral DNA, we analyzed the relative rates of transcription of MTV and adjacent HTC sequences in two lines of infected HTC cells, J2.15 and J2.17, each of which contains a single insertion of MTV DNA. In addition, we measured in uninfected HTC cells the transcriptional rates of the corresponding 'preinsertion fragments,' which may be viewed as the equivalent sequences bearing deletions of MTV DNA; the two genomic segments into which integration occurred in the two lines are unrelated. Previous work showed that glucocorticoids induce the accumulation of MTV RNA in J2.17, whereas viral transcripts are not detected in J2.15. RNA pulse-labeling experiments indicate that glucocorticoids stimulate the rate of MTV gene transcription in J2.17 but not in J2.15; in contrast, no labeled RNA hybridizing to flanking sequences was detected either in the uninfected or in the infected cells. We conclude that the host site of integration of MTV need not be transcriptionally active or hormonally responsive to permit viral gene expression. Furthermore, these rate measurements indicate that glucocorticoid-stimulated MTV RNA synthesis in J2.17 does not reflect readthrough transcription from a regulated cellular promoter. This notion is independently supported by transcript mapping experiments showing that the 5' terminus of nuclear MTV RNA is at a site on MTV DNA approx 1.2 kb downstream from the host-viral junction. Thus our data are consistent with the presence of a hormone-responsive element within the provirus. (Author abstract) (32 Refs)

41. SUBSTRATE SPECIFICITY OF HUMAN UDP-GLUCURONYLTRANSFERASE IN CULTURED LYMPHOCYTES.

Li HC, Porter N, Holmes G, Gessner T
Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
Xenobiotica; 11(10):647-654 1981

This study establishes the presence of UDP-glucuronyltransferase activity for non-steroidal as well as steroidal substrates, in cultured human B-lymphocytes. Glucuronidation of alpha-naphthol and testosterone was demonstrated in homogenates of two cell lines, SN1006 and RPMI-1788, and that of phenolphthalein, 4-methylumbelliferone, p-nitrophenol and estradiol in the cell line with the higher glucuronyltransferase activity, SN1006. Kinetic studies of testosterone glucuronidation in homogenates of both cell lines revealed a similarity in the behavior of glucuronyltransferase of these cells. Thus, comparable apparent Km values for UDPGA (0.63 mM) and for testosterone (14 uM) were observed, although apparent maximal velocities, Vmax, differed several-fold (3.0 vs 0.55 pmol/10(6) cells per min, in SN1006 and RPMI-1788 cells, respectively). Kinetic studies of glucuronidation of testosterone, estradiol, phenolphthalein, alpha-naphthol, 4-methylumbelliferone, and p-nitrophenol yielded comparable apparent Km values for UDPGA (0.56-0.67 mM), suggesting that the same, or similar, glucuronyltransferase(s) catalyze(s) glucuronidation of this wide range of substrates in lymphocytes. This was reinforced by the observation of competitive inhibition of testosterone glucuronidation by alpha-naphthol (Ki 0.25 mM), 4-methylumbelliferone (Ki 0.8 mM) and p-nitrophenol (Ki 0.8 mM). Thus, lymphocyte glucuronyltransferase activity with a broad substrate specificity, for steroidal and non-steroidal aglycones, is indicated. (Author abstract) (30 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

42. HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED EPITHELIAL OVARIAN CANCER RESISTANT TO FIRST- OR SECOND-LINE CHEMOTHERAPY.

Mangioni C, Franceschi S, La Vecchia C, D'Incalci M
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Gynecol Oncol; 12(3):314-318 1981

Out of 33 evaluable patients with advanced ovarian cancer, resistant to extensive polychemotherapy, then treated with high-dose im medroxyprogesterone (MPA), five partial responses (15%) were obtained. No partial response was obtained in a comparable group of 30 patients treated with an oral schedule. Four patients (2 po, 2 im) had stable disease for at least 3 mo, and 16 experienced subjective improvement. Treatment was very well tolerated. This study shows that high-dose MPA has some activity in ovarian cancer, and is worthy of further investigation. (Author abstract) (7 Refs)

43. THE ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF BREAST CANCER AND ENDOMETRIAL CARCINOMA.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Rev Bras Clin Ter; 10(9):671-678 1981

The roles of estrogens and progestogens in mammary and endometrial cancers were presented under the following headings: role of exogenous estrogens in endometrial cancer (EC), role of endogenous estrogens in EC, role of oral contraceptives (OCs) in EC, role of exogenous estrogens in mammary cancer (MC), role of endogenous estrogens in MC, and role OCs in MC. Administration of estrogen plus progestogen (EP) to menopausal women decreases the incidence of EC below that of untreated women. Postmenopausal women with increased endogenous estrogens should receive progestogens to reduce the risk of EC. OCs with EP in every tablet are protective against EC, while sequential administration provided less protection. MC is significantly less frequent in women receiving estrogens or EP than in postmenopausal women that never receive the hormones. OCs reduce the risk of benign mammary disease and give some protection against MC. Mortality rate due to MC is significantly lower in women who used OCs than in those who did not. (34 Refs) (In POR)

44. EFFECTS OF POSTOPERATIVE ADJUVANT CHEMOTHERAPY AND RADIOTHERAPY ON OVARIAN FUNCTION IN WOMEN UNDERGOING TREATMENT FOR SOFT TISSUE SARCOMA.

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JNCI; 67(6):1213-1218 1981

Ovarian function was evaluated in 11 women 16 to 43 yr of age at treatment who received doxorubicin, cyclophosphamide, and high doses of methotrexate with or without radiotherapy in adjuvant therapy of soft tissue sarcoma. Five women (16-33 yr old) who received chemotherapy alone or combined with radiotherapy only at sites distant from the ovaries (chest wall, thigh, and leg) had minimal menstrual irregularities or temporary cessation of menses during therapy; cyclic menses returned promptly after therapy. Gonadotropin levels (expressed as means +- SD) [follicle-stimulating hormone (FSH), 10 +-5 mIU/ml; luteinizing hormone (LH), 10 +-4 mIU/ml] and 17beta-estradiol (E2) levels (means +- SD, 208 +-147 pg/ml) were normal. By contrast, four older women (ages 36-43 yr) who received similar treatment developed persistent amenorrhea with postmenopausal levels of gonadotropin (FSH, 108 +-29 mIU/ml; LH, 72 +-19 mIU/ml) and E2 (19 +-8 pg/ml). Two additional women (ages 21 and 39 yr) who received radiation (7,000 rad) to the pelvis plus chemotherapy developed prompt cessation of menses and became functional castrates (FSH, 77 and 80 mIU/ml; LH, 40 and 58 mIU/ml; E2, 10 and 19 pg/ml). However, this result would be expected from the radiation dose alone. The data demonstrated that ovarian dysfunction may follow the use of doxorubicin, cyclophosphamide, and high doses of methotrexate and that the injury is age related. (Author abstract) (35 Refs)

45. ENDOCRINE ASSESSMENT IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA.

Fisher JN, Aur RJ
Dept. Medicine, Univ. Tennessee Center for Health Sciences, 951 Court Ave., Memphis, TN, 38163
Cancer; 49(1):145-151 1982

Ten children ages 7 to 18 (8 girls, 2 boys) with acute lymphoblastic leukemia (ALL) were studied. Remission was induced with prednisone, vincristine, and asparaginase followed by preventive central nervous system treatment with 2,400 rads cobalt-60 cranial irradiation plus intrathecal methotrexate. At the time of study all patients had been on continuation chemotherapy with two to four drugs for 2 to 2 1/2 years. Three patients were on mercaptopurine and methotrexate, one was on cyclophosphamide in addition, and six were on these drugs plus arabinosyl cytosine. Linear growth and bone age for height was appropriate in all. Tests included oral glucose (OGTT) and tolbutamide (TOLB) tolerance tests, ACTH infusion, thyroid function and measurement of noctural growth hormone (IRGH), and cortisol. All patients tested (9/10) had a normal OGTT. Peak glucose and insulin (IRI) values occurred at 30 minutes in 8/9 subjects (IRI range 24-143 uU/dl). IRGH responses to sleep, TOLB and following OGTT were greater than 5 ng/ml in at least one test in all, with 5/10 patients responding above this level in all three tests. Diurnal variation of cortisol was observed in all patients (8/10) studied. Thyroid function and response to ACTH was normal in all patients. No consistent changes were observed in gonadotropins. It is concluded from these results that hypothalamic pituitary function appeared to be intact despite 2,400 rads of cobalt-60 cranial radiation and ongoing chemotherapy for ALL in 10 patients observed. Long-term studies are required to exclude late endocrine complications in such children. (Author abstract) (25 Refs)

46. CELL CYCLE-SPECIFIC GLUCOCORTICOID GROWTH REGULATION OF A HUMAN CELL LINE (NHIK 3025).

Bakke O, Eik-Nes KB
Inst. Biophysics, Univ. Trondheim, 7034 Trondheim-NTH, Norway
J Cell Physiol; 109(3):489-496 1981

Cells, synchronized by mitotic selection, were exposed to dexamethasone (DEX) throughout the cell cycle. Cells exposed during the first half of G1 had lengthened cell cycle time, and most of the prolongation occurred in that phase. Exposure during other phases was ineffective. The growth inhibition was reversible, but did not extent to subsequent cell cycles where there was no exposure to DEX. (23 Refs)

47. INTEREST IN HIGH DOSE CORTICOTHERAPY IN TERMINAL CANCER PATIENTS.

Bourhis A, Boutin C, Catel P, D'Estienne d'Orves JF, Germouty J, Gestin Y, Happert JL, Namer M, Segalovitch JF
Institut Paoli-Calmettes de Marseille, Marseille, France
Gaz Med Fr; 88(31):4384-4394 1981

Six hundred sixty-five cancer patients (343 women, 322 men; 28-94 yr old) who were considered to be incurable underwent palliative therapy with high dose 6-alpha-methyl-prednisolone (AMPD). AMPD treatment reduced peri-tumoral edema and the resultant functional difficulties. Notable pain relief was noticed in 79% of the patients based on questioning, spontaneous declaration, and requests for pain medications. Relief of cachexia was observed in 85% of the patients. Further indication of AMPD-induced pain relief was increased and improved activity levels. AMPD treatment improved the emotional status in 543/665 patients. Following AMPD treatment, many biochemical parameters were normalized as evidenced by decreases in sedimentation speeds, alkaline phosphatase levels, alpha-2-globulins, and hypercalcemia. Improvements were noted with regard to biological tumor markers in 15% of the patients following AMPD treatment. Complications of AMPD therapy included hypertension (5% of patients), steroid diabetes (8%), potassium loss (2%), water-electrolyte retentions (1%), capillary fragility (15%), infections (12%), and adrenal gland and hypophyseal disorders (0.8%). Hypercorticism related to AMPD use is discussed. Results indicated that AMPD is well-tolerated and useful in the treatment of terminal cancer patients. (22 Refs) (In FRE)

48. HOW EFFECTIVE IS SURGICAL ADRENALECTOMY IN LOWERING STEROID HORMONE CONCENTRATIONS?

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J Clin Endocrinol Metab; 54(1):22-26 1981

Surgical adrenalectomy produces objective tumor regression in 50-60% of estrogen receptor-positive women with metastatic breast carcinoma. Additional responses to antiestrogens or further suppression of estrogens with aminoglutethimide after adrenalectomy suggest the possibility of continued adrenal steroid secretion even after surgical ablation. The use of sensitive and specific RIAs allows precise determination of the degree of hormone suppression after adrenalectomy and could provide documentation of nonsuppression or escape from suppression in individual patients. To evaluate the possibility of continued hormone secretion, we measured 14 hormones in 26 postmenopausal women with breast carcinoma before and after adrenalectomy. While the mean levels of androgens were markedly suppressed after adrenalectomy, estrogen concentrations fell to a much lesser extent. Examination of data in individual patients revealed incomplete suppression in several women. Androgen concentrations also fell incompletely after adrenalectomy in a few patients. Androstenedione concentrations were greater than 2 SD above the group mean in 2 of 23 patients, and in 2 of 25 patients, DHEA-S concentrations were also greater than 2 SD above the group mean. Serial measurements of hormones over a 1-to 3-yr period following surgery revealed escape from suppression over time in 7 of 26 women. The practical significance of the lack of suppression or of escape from inhibition was assessed by comparing estrogen levels in respondes vs nonresponders to surgical adrenalectomy. Of all steroids measured, greater suppression of only one hormone was observed in responders vs. nonresponders. These data indicate that adrenalectomy does not uniformly suppress circulating androgen and estrogen levels in postmenopausal patients. Women who initially suppress after adrenalectomy may show recovery of either androgen or estrogen levels with time. (24 Refs)

49. ANALYSIS OF THE ANDROGEN RESPONSE OF 23 PATIENTS WITH AGNOGENIC MYELOID METAPLASIA: THE VALUE OF CHROMOSOMAL STUDIES IN PREDICTING RESPONSE AND SURVIVAL.

Besa EC, Nowell PC, Geller NL, Gardner FH
Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129
Cancer; 49(2):308-313 1982

The responses of 23 patients with agnogenic myeloid metaplasia (AMM) to androgen therapy were studied. Various clinical and laboratory parameters were analyzed for their value in determining response to therapy and length of survival. Fifty-seven percent of patients responded, as determined by a sustained increase in hematocrit within 3 mo of therapy which thus eliminated the need for transfusions. Chromosome study of the abnormal hemic population was the best predictor of response: 92% of patients with normal chromosomes responded, while 78% of patients with chromosomal abnormalities did not. Responders had a mean survival time of 5 1/2 yr from the time of diagnosis as compared with 2 yr for the nonresponders. The degree of thrombocytopenia, suppression of the ferrokinetic, and lack of activity in axial skeleton on bone marrow scans indicated severly compromised hemopoiesis in the nonresponders. The results suggest that in some patients with AMM, more extensive cytogenetic alterations in the abnormal hematopoietic cells result in an inability to respond to androgen therapy and that the chromosome study is the test most accurate for predicting the outcome of therapy. (Author abstract) (29 Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

50. SPECIFIC IMMUNOADSORPTION OF IGG ANTIBODY IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND AUTOIMMUNE HEMOLYTIC ANEMIA: A NEW FORM OF THERAPY FOR THE ACUTE CRITICAL STAGE.

Besa EC, Ray PK, Swami VK, Idiculla A, Rhoads JE, Bassett JG, Joseph RR, Cooper DR
Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129
Am J Med; 71(6):1035-1040 1981

Progressive and severe autoimmune hemolytic anemia developed in a patient with chronic lymphocytic leukemia (CLL) despite treatment with chlorambucil, high doses of corticosteroids and attempts to transfuse packed red blood cells. Splenectomy was not performed because of severe coronary artery disease. Direct antiglobulin tests revealed a warm red blood cell autoantibody of IgG-type with anti-e specificity. The patient was treated by extracorporeal immunoadsorption of plasma IgG using a cell separator and protein A as the immunoadsorbent. The patient responded by an increase in the hemoglobin levels and platelet counts after two treatments. Specificity of the procedure was shown by a decrease in the serum IgG and by the demonstration of the same reactivity to ficin-treated reagent red blood cell panel of the eluate from the protein A. Antibody titers of the patient's red blood cell eluate decreased from 1:128 to 1:64 and eventually the anti-e specificity was lost. This is a report of a novel approach to treatment of the acute phase of an autoimmune hemolytic anemia. (Author abstract) (22 Refs)

GENERAL REVIEWS ON STEROID HORMONES

51. ESTROGEN RECEPTOR CYTOCHEMISTRY IN HUMAN BREAST CANCER: STATUS AND PROSPECTS.

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Istituto Anatomia Patologica, Universita di Ferrara, Ferrara 44100, Italy
Cancer; 48(12):2674-2686 1981

Advances in knowledge of the endocrine control of neoplastic growth can be expected to stem directly from advances in pertinent techniques. Following this theme, the present paper describes how recent development in cytochemical techniques for estrogen receptors may maintain this expectation and lead to significant progress in the basic knowledge of breast cancer that can influence the treatment approach. Cytochemical techniques have shown that the binding of estrogen to target cells and tissues can be specifically visualized: moreover, estrogen binding sites characterized cytochemically under controlled conditions have proved to fulfill the accepted criteria for estrogen receptors. Some working solutions to basic questions concerning the tumor hormone-responsiveness have been provided and more precise explanations of fundamental growth-regulatory mechanisms are expected to emerge from the approach to breast cancer by cytologic endocrinology. However, in the present state of the art and in spite of tantalizing bits of data, cytochemical techniques for estrogen receptors do not seem extensible to routine purposes, as alternative to biochemical receptor assays in selecting patients for endocrine therapy. One must have strong reservations on their clinical use because of the almost complete lack of information about correlations of cytochemical results with the response to endocrine therapy. More studies evaluating the practical validity of estrogen receptor cytochemistry are required. (Author abstract) (92 Refs)

52. PRIMARY GASTRIC CHORIOCARCINOMA: IMMUNOHISTOCHEMISTRY, POSTMORTEM DOCUMENTATION, AND HORMONAL EFFECTS IN A POSTMENOPAUSAL FEMALE.

Wurzel J, Brooks JJ
Hosp. Univ. Pennsylvania, 3400 Spruce St., Philadelphia, PA, 19104
Cancer; 48(12):2756-2761 1981

A rare tumor, primary choriocarcinoma of the stomach, occurred in a post menopausal female. The diagnosis was confirmed by autopsy and by immunohistochemical demonstration of HCG in trophoblastic tumor cells. Theories concerning development of this neoplasm are briefly discussed. In addition, this postmenopausal case uniquely permitted examination of the hormonal effects of the tumor on target tissues without the clouding issue of normal menstrual hormones. It appears that the observed estrogen- and progesterone-related tissue responses were not mediated through the ovary; instead, direct tumor production of these hormones is implicated. (Author abstract) (29 Refs)

53. CONTRACEPTIVES AND THE LIVER.

Schmid M
Medizinische Klinik, Stadtspital Waid, Tiechestr. 99, CH-8037 Zurich, Switzerland
Leber Magen Darm; 11(5):216-226 1981

Studies on the relationships between the use of oral contraceptives (OC) and hepatic diseases are reviewed. The relationship between the long-term use of OC and benign hepatocellular adenoma is now beyond doubt. The progestagen component of the ovulation inhibitor acts as an enzyme inducer which may facilitate the formation of carcinogenic metabolites from various substances, and prompt elimination of these metabolites with the bile is prevented by the cholestatic effect of the estrogens. The relationship between OC and focal nodular hyperplasia is less evident. Here, the congenital hamartomatosis represents a site of least resistance for the hormones, but the steroid hormones are probably responsible for the vascular complications, especially for peliosis. Malignant hepatic tumors (hepatocellular carcinoma and especially hepatoblastoma and angiosarcoma) in connection with the long-term use of OC are extremely rare. The alpha-fetoprotein level is usually not increased significantly in patients with hepatocellular adenoma and carcinoma due to OC. (52 Refs) (In GER)

54. HEPATIC LESIONS CAUSED BY ANABOLIC AND CONTRACEPTIVE STEROIDS.

Ishak KG
Dept. Hepatic Pathology, Armed Forces Inst. Pathology, Washington, DC
Semin Liver Dis; 1(2):116-128 1981

The pathobiology of hepatic lesions induced by long-term use of contraceptive (CS) or anabolic (AS) steroids is described. Lesions attributable to CS and AS may involve any of the systems of the liver, from the bile canaliculi to the hepatocyte to the vessels supplying and draining blood. Oral contraceptives have a number of physiologic effects upon the liver which include decreased bile flow, diminished secretion of organic anions and decreased synthesis and secretion of bile acids. Estrogens and progestins can increase the activity of many enzymes and alter the concentration of many plasma proteins. Subcellular alterations have been reported in humans and rats on AS and women on CS and involve multiple organelles of the several systems of the liver. Both AS and CS have been implicated in intrahepatic cholestasis, and in vascular complications including sinusoidal dilatation, peliosis hepatis, and Budd-Chiari syndrome. AS and CS have been associated with diffuse hyperplasia, nodular transformation, focal nodular hyperplasia, hepatocellular adenoma, hepatocellular carcinoma, and miscellaneous malignant tumors. Nonneoplastic effects include potentiation of preexisting liver disease, cholelithiasis, and pancreatitis. (167 Refs)

55. TOXIC AND METABOLIC LIVER INJURY.

Teschke R, Nishimura M, Gellert J
Medizinische Klinik D, Universitat Dusseldorf, Moorenstr. 5, D-4000 Dusseldorf, W. Germany
Leber Magen Darm; 11(5):227-234 1981

Studies on liver damage due to toxic substances and endogenous metabolites are reviewed. Liver cirrhosis due to phenylbutazone, dantrolen, diazepam, isoniazid, alpha-methyldopa, oxyphenisatin, azathioprin, mercaptopurine, methotrexate (MTX), and methyltestosterone was observed. Focal nodular hyperplasia due to oral contraceptives (ethinyl estradiol, mestranol, norethynodrel and norgestrel) was reported in the literature. These oral contraceptives, as well oxymetholone and methyltestosterone were found to induce hepatocellular adenoma. Hepatocellular carcinoma was found in patients treated with MTX, oral contraceptives, oxymetholone and methandrostenolone. (24 Refs) (In GER)

56. MOLECULAR BASIS OF STEROID HORMONE ACTION IN BREAST CANCER AND ITS CLINICAL IMPLICATIONS.

Lunenfeld B, Geier A
Inst. Endocrinology, Chaim Sheba Medical Center, 52103 Tel-Hashomer, Israel
Isr J Med Sci; 17(9/10):954-959 1981

The measurement of steroid hormone receptors in tumors from patients with breast cancer is now established. Data have accumulated that seem to indicate that breast cancer patients may be selected for endocrine or adjuvant therapy on the basis of the presence or absence of estrogen receptors. Furthermore, patients without detectable estrogen receptors seem to have a greater likelihood of early recurrence following mastectomy. We describe recent findings on the mechanism of action of both estrogens and antiestrogens at the normal target cell level. Evidence for a similar mechanism of action for estrogens and antiestrogens in the hormone-responsive mammary tumor cell is presented on the basis of studies in hormone-dependent, dimethylbenz(a)anthracene-induced mammary carcinoma in the rat, and the cell line MCF-7 derived from a human breast carcinoma. The interaction of estrogens and antiestrogens with their receptors in the cytoplasm and nucleus in solid human breast tumors is discussed and analyzed in terms of the potential clinical application to breast cancer management. (Author abstract) (54 Refs)

57. ADJUVANT CHEMOTHERAPY OF MAMMARY CARCINOMA.

Senn HJ
Medizinische Klinik C, Kantonsspital, Rorschacherstr. 95, CH-9007 St. Gallen, Switzerland
Dtsch Med Wochenschr; 106(48):1626-1630 1981

The status of adjuvant chemotherapy in treatment of mammary carcinoma (MC) is reviewed. Retrospective and prospective studies indicate that survival time and risk of recurrence depend in large measure on involvement of homolateral axillary lymph nodes. Because local treatment (surgery and radiotherapy) have had little success in controlling micrometastases, recent emphasis has been on developing systemic chemotherapeutic treatments. Cytostatic agents in use include cyclophosphamide (CP), methotrexate (MT), fluorouracil (FU), vincristine (VC), chlorambucil (CA), and adriamycin (ADM). Combination regimens include CMF (CP, MT, and FU), LMF (CA, MT, and FU), AC (ADM and CP), and FAC (FU, ADM, and CP). Clinical studies comparing results of surgical treatment with those of surgery with adjuvant chemotherapy indicate that mono- or polychemotherapy significantly increases recurrence-free survival time. LMF in combination with immunotherapy provides the best results in patients with lymph node metastases, except in those with four or more involved axillary nodes. Studies to evaluate the effects of chemo- and hormonal therapies in pre- and post-menopausal patients, and to clarify the significance of estrogen receptors are currently under way. (31 Refs) (In GER)

OTHER RELATED STUDIES

58. HISTOLOGICAL EVIDENCE OF 'ESTROGENIC PROPERTIES' OF 7-12 DIMETHYLBENZ(A)ANTHRACENE.

Valero D, Drouhault R, Vanhems E, Bousquet J, Blanquet P
Unite 53, I.N.S.E.R.M., Domaine de Carreire, Rue Camille Saint-Saens, 33077 Bordeaux Cedex, France
Cell Mol Biol; 27(2/3):263-269 1981

DMBA (7,12 dimethylbenz(a)anthracene) and estradiol provoke in rat pituitaries an increase of prolactin cells number and of hormone synthesis. It is a transitory effect. Both enhance equally G6PD activity, this enzyme acting for an end product of a functional estradiol receptor. This increased reactivity persists during mammary tumor growth. These data added to previously published results, support the hypothesis that carcinogen would act in part by 'estrogen-mimetic' properties. (Author abstract) (25 Refs) (In FRE)

59. PERSISTENCE OF CUSHING'S SYNDROME AFTER HYPOPHYSECTOMY.

Federman DD, Mark EJ, Simeone JF, Ridgway EC, Scully RE, Daniels GH, Calderwood SB
Professor Medicine, Harvard Medical Sch., MA
N Engl J Med; 305(27):1637-1643 1981

Case history, discussion, and differential diagnosis of a patient (male, 23 yr old) with suspected Cushing's syndrome are presented. Symptoms were puffy appearance, decreased muscle strength, easy bruising, and a slight increase in wt. Physical examination revealed hypertension, tremor of the hands, pink striae over the buttocks, and pedal edema. Earlier tests had shown the fasting cortisol level to be 20 ug/100 ml and the fasting ACTH level 102 picog/ml. An x-ray of the chest had revealed a 1.5 cm nodule. Further tests revealed abnormal response in human growth hormone (less than 1-1.8 nanog/ml), thyroid stimulating hormone (2.5-3.8 microU/ml), prolactin (4.9-4.7 nanog/ml), and cortisol secretion (47-56 ug/100 ml). A transsphenoidal operation was performed and an apparent microadenoma was removed. The symptoms persisted and the patient was maintained on prednisone, levothyroxine, propranolol, and chlorthalidone. After discontinuation of prednisone and levothyroxine the patient developed mild muscular weakness, cold intolerance, coarse, dry skin, and arthralgia of the knees and fingers. Serum cortisol and plasma ACTH levels ranged from 8.0-10.0 ug/100 ml and 28-53 picog/ml, respectively; after dexamethasone therapy they decreased to 0.7 ug/100 ml and 7 picog/ml, respectively. Clinical diagnosis was Cushing's syndrome secondary to bronchial carcinoid. Follow up after tumor extraction revealed extremely high levels of ACTH. Cortisol levels remained low; prednisone therapy was instituted and tapered over 3-4 mo and then discontinued. The patient is now normal biochemically and has lost many of the cushingoid features. (25 Refs)

60. STRUCTURAL GENE PRODUCTS OF THE AH LOCUS. EVIDENCE FOR MANY UNIQUE P-450-MEDIATED MONOOXYGENASE ACTIVITIES RECONSTITUTED FROM 3-METHYLCHOLANTHRENE-TREATED C57BL/6N MOUSE LIVER MICROSOMES.

Lang MA, Nebert DW
Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Biol Chem; 256(23):12058-12067 1981

Cytochrome P-450 from cholate-solubilized liver microsomes prepared from 3-methylcholanthrene-treated genetically 'responsive' C57BL/6N mice (Ahb/Ahb) was partially purified by aminooctyl-Sepharose 4B column chromatography with an elution buffer that included Emulgen 911, followed by hydroxylapatite column chromatography. The P-450 was separated into 16 fractions: 15 fractions principally associated with the Ahb allele and induction by 3-methylcholanthrene and 1 fraction not associated with the Ahb allele, ie predominantly constitutive form(s) of P-450. The metabolism of benzo[a]pyrene, 7-ethoxycoumarin, biphenyl, ethoxyresorufin, acetanilide, 2-acetylaminofluorene, phenacetin, estradiol-17beta, and testosterone was investigated. With these nine substrates, we examined the rates of formation of 17 products, ie 17 P-450-mediated reconstituted monooxygenase 'activities,' in each of the 16 fractions. Differing reductase/cytochrome and lipid/cytochrome requirements were observed for each activity; the reasons for these empirical differences are not known. By two-factor analysis of variance, our data for 17 catalytic activities can be explained by a minimum of 19 unique groups of monooxygenase activities: 12 induced by 3-methylcholanthrene and 7 control (endogenous). At least one of these distinctly different 3-methylcholanthrene-induced groups and at least one of these constitutive groups is associated with a marked blue spectral shift (approx 2.0 nm) in the Soret peak of the reduced hemoprotein-CO complex, suggesting multiple forms of inducible and control 'P-448.' Almost every reconstituted monooxygenase activity therefore appears to be unique and probably represents the aggregate activity from numerous forms of P-450. (Author abstract) (43 Refs)

61. PEROXIDASE ACTIVITY AS A MARKER FOR ESTROGENICITY: STUDIES IN UTERUS AND MAMMARY TUMORS.

Levy J, Liel Y, Glick SM
Dept. Endocrinology, Soroka Medical Center, 84101 Beersheba, Israel
Isr J Med Sci; 17(9/10):970-975 1981

We examined the possibility that peroxidase activity might be a marker for estrogen activity in established estrogen-dependent tissues: dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumors and human breast cancer. In DMBA-induced tumors undergoing regression after ovariectomy or tamoxifen treatment, tumor size decreased by 50%, estradiol receptors (ER) and progesterone receptors (PgR) decreased by 25 and 20%, respectively, but peroxidase activity paradoxically increased six- to sevenfold. In DMBA tumors stimulated by estradiol treatment or by the cessation of tamoxifen administration in intact rats, tumor size increased threefold. ER and PgR increased two- and threefold, respectively, while peroxidase activity decreased 50%. These data indicate an inverse relation between tumor growth, ER and PgR on the one hand, and peroxidase activity on the other. In the human breast cancers there was a significant negative relation between the presence of ER and peroxidase activity. By using a calibrated Sephadex G-100 column it was shown that uterine peroxidase differs in molecular weight from the peroxidase of rat mammary tumors and that of human breast cancer. (Author abstract) (21 Refs)

62. INHIBITION OF COLLAGEN ACCUMULATION BY GLUCOCORTICOIDS IN RAT LUNG AFTER INTRATRACHEAL BLEOMYCIN INSTILLATION.

Sterling KM, DiPetrillo T, Cutroneo KR, Prestayko A
Coll. Medicine, Univ. Vermont, Burlington, VT, 05405
Cancer Res; 42(2):405-408 1982

Male Fischer 344 rats were given a single lung instillation of bleomycin sulfate (0.6 units/100 g). Some animals were treated 24 hr after bleomycin administration with triamcinolone diacetate. Steroid treatment was continued on alternate days for 4 weeks. At the end of 4 weeks, the lungs of rats receiving bleomycin alone had two-fold increases of both prolyl hydroxylase activity and proteinaceous hydroxyproline as compared to control values. The lungs of bleomycin-treated rats which received 4 mg of triamcinolone diacetate per kg on alternate days had a 33% increase of prolyl hydroxylase activity and a 37% increase of proteinaceous hydroxyproline content as compared to control values. Lung prolyl hydroxylase activity and proteinaceous hydroxyproline content of bleomycin-treated animals receiving glucocorticoid (8 mg/kg) on alternate days were the same as control values. The results indicate that alternate day administration of the synthetic glucocorticoid triamcinolone diacetate blocks lung collagen accumulation following a single intratracheal dose of bleomycin to rats. (Author abstract) (38 Refs)

63. EFFECTS OF ETHYNYLESTRADIOL ADMINISTRATION ON GONADOTROPIN LEVELS AND CLINICAL EVALUATIONS IN PATIENTS WITH PROSTATIC CANCER.

Maruta H, Kumamoto Y
Dept. Urology, Sapporo Medical Coll., Sapporo, Japan
Hinyokika Kiyo; 27(9):1133-1142 1981

Serum LH and FSH were measured by radioimmunoassay in five patients with prostatic cancer following castration and oral ethynylestradiol administration. Serum acid phosphatase levels of 10 patients were also examined to evaluate the clinical efficacy of ethynylestradiol for treating the prostatic cancer. Of four castrated patients who received the ethynylestradiol at the dose of 0.15 mg/day for 10-14 days, LH and FSH levels of two patients were suppressed significantly, but were not suppressed to the level of prepubertal value. LH and FSH of two other patients were not suppressed at the dose of 0.15 mg/day. To suppress the gonadotropin of castrated male completely to the prepubertal level, it was needed to administer the ethynylestradiol at the dose of 1.5 mg/day for about 20 days. Of nine patients who showed the elevated acid phosphatase level before treatment, one patient showed normal level after castration, the acid phosphatase levels of five other patients became normal following the castration and ethynylestradiol administration. From the finding of normal acid phosphatase level following ethynylestradiol administration, ethynylestradiol was considered to be the effective drug for the prostatic cancer. (Author abstract) (11 Refs) (In JPN)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. EFFECT OF CADMIUM ON ANDROGEN LEVEL AND OXIDOREDUCTIVE ENZYMES ACTIVITY IN CULTURED LEYDIG CELLS OF KP AND CBA MICE.

Godowicz B, Bilinska B
Dept. Genetics and Evolution, Jagellonian Univ., 30-060 Cracow, Poland
Folia Histochem Cytochem (Krakow); 19(4):197-207 1981

Androgen level and the activity of lactate dehydrogenase, succinic dehydrogenase, 17beta-hydroxysteroid dehydrogenase and NADP-diaphorase was studied in cultured Leydig cells obtained from testes of male mice from inbred strains KP and CBA following a single injection of cadmium chloride. Mice

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from CBA strain, known to be resistant to the toxic effects of cadmium showed no differences in the enzyme ac tivity and endocrine function of gonads, as compared with control animals. In KP mice, sensitive to cadmium, a marked decrease of activity of all studied dehydrogenases, as well as a fall of androgen level was observed following cadmium administration. The decrease of hormone secretion occurred on the 2nd day of tissue culture and showed a correlation with the 17beta-hydroxysteroid dehydrogenase activity. (Author abstract) (17 Refs)

2. PROGESTERONE SYNTHESIS, SECRETION AND METABOLISM BY HUMAN TERATOMA-DERIVED CELL-LINES.

O'Hare MJ, Nice EC, McIlhinney RA, Capp M
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Steroids; 38(6):719-737 1981

The synthesis, secretion and metabolism of progesterone have been examined in six human teratoma-derived cell lines with the objective of determining if they exhibit trophoblast-related or other specific steroidogenic functions. Progesterone was synthesized in nanogram amounts (per 10(6) cells/day) by the cell line SuSa, as measured by radioimmunoassay, and in lesser amounts by line LICR-LON HX-39. Lines Tera 1, Tera 2, T3B1 and PA-1 did not secrete detectable progesterone. All teratomas, however, metabolized added progesterone in microgram amounts (per 10(6) cells/day). In all cases the major metabolite was a polar compound, identified by reversed phase HPLC, TLC and GC-MS as 3beta, 6alpha-dihydroxy-5alpha-pregnan-20-one. This pattern of metabolism was not confined to the teratomas as equivalent amounts of this polar metabolite were formed by cultures of adult differentiated human epithelial and fibroblast cells. When progesterone and its metabolites, separated by HPLC, were included in the estimation, the delta(5)-3beta-hydroxysteroid dehydrogenase-isomerase activity of SuSa was equivalent to 47ng prognenolone (3beta-hydroxy-5-pregnen-20-one) metabolized/mg protein/day, that of HX-39 to 9 ng/mg protein/day and those of other teratomas to less than 3.5 ng/mg protein/day. (Author abstract) (41 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

3. ESTRAMUSTINE BINDING IN RAT, BABOON AND HUMAN PROSTATE MEASURED BY HIGH PRESSURE LIQUID CHROMATOGRAPHY.

Kirdani RY, Corrales JJ, Hoisaeter PA, Karr JP, Murphy GP, Sandberg AA
Roswell Park Memorial Inst., Buffalo, NY, 14263
Steroids; 37(5):471-484 1981

High pressure liquid chromatography (HPLC) was used to determine 3H-estramustine (estradiol-17beta3N-bis-[2-chlorethyl] carbamate), 3H-17beta-hydroxy-5-alpha-androstan-3-one (3H-dihydrotestosterone or 3H-DRT), 3H-estradiol-17beta (3H-E2) and 3H-3beta-hydroxy-5-pregnen-20-one [3H-pregnenolone] binding in 50 ul of cytosol utilizing a column which separates proteins in the mol wt range of 2,000 to 70,000 daltons. The rat prostate contains a protein in considerable concentration and with the highest affinity for estramustine (375,000 dpm 3H-estramustine per mg cytosol protein) among the substances tested. Operationally, we have named this protein 'estramustine binding protein' (EBP), though it is very likely similar to other previously described prostatic proteins eg, alpha-protein, prostatein prostatic binding protein). The sensitivity of the HPLC method disclosed EBP-like proteins, but in much lesser concentratons, in some of the other tissues tested. The concentration of these proteins in the human and baboon prostates was much lower (av for the baboon cranial lobe 4,800 dpm/mg cytosol protein, with a somewhat higher value for the caudal lobe) than that in the rat gland. The amount of EBP-like protein was higher in prostatic cancer than in that of benign prostatic hypertrophy (range 9,350-25,900 vs 2,200-18,900 dpm/mg cytosol protein). In the human, the highest value was found in one normal prostate tested (106,000 dpm/mg cytosol protein). (Author abstract) (13 Refs)

4. RAPID ANALYSIS OF ESTROGEN AND PROGESTERONE RECEPTORS USING GEL-EXCLUSION HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY.

Pavlik EJ, Von Nagell JR, Muncey M, Donaldson ES, Hanson M, Kenady D, Rees ED, Talwalkar VR
Dept. Obstetrics and Gynecology, Univ. Kentucky, Albert B. Chandler Medical Center, Lexington, KY, 40536
Biochemistry; 21(1):139-145 1982

Estrogen and progesterone receptors prepared from mouse, rat, and human uteri, as well as from human breast cancers, have been characterized by gel-exclusion high-performance liquid chromatography. The qualitative relationships previously established by sedimentation analysis between the cytoplasmic [aggregated (approx 8S), deaggregated (approx 4S), and trypsinized (approx 3.6S)] and nuclear (approx 5S) forms of the rat uterine estrogen receptor were maintained by this technique. Differences in the partition of estrogen and progesterone receptors from the same species as well as interspecies differences in these receptors were reproducibly observed. Multiple forms of human estrogen and progesterone receptors could clearly be resolved in a single analysis and were distinct from serum steroid binding tissue contaminants. Separation analyses, performed at flow rates up to 2 mL min-1, were capable of resolving all receptor forms in 10-12 min with the column returning to base line in 25 min. With this exclusion gel column (TSK-G3000SW) as a background upon which to reference different receptor forms, eight distinct partitions or elution positions have been enumerated. This approach has considerable promise for the rapid characterization of different forms of steroid-receptor proteins. Moreover, it should provide a critical advantage in minimizing the opportunities for receptor modification during separation analysis and in maximizing the opportunity to study short-lived interactions between receptors and physiologic or pharmacologic ligands. (Author abstract) (37 Refs)

5. THE EFFECTS OF HODGKIN'S DISEASE AND COMBINATION CHEMOTHERAPY ON GONADAL FUNCTION IN THE ADULT MALE.

Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG
(c/o Shalet) Dept. Endocrinology, Christie Hosp., Wilmslow Road, Manchester M20 0BX, England
Cancer; 49(3):418-422 1982

The effects of Hodgkin's disease and quadruple chemotherapy on gonadal function have been investigated in 93 male patients with Hodgkin's disease. Nineteen men were studied before they received chemotherapy. Fifteen of the 19 had a sperm count of 20 million/ml or greater and motility was at least 40% in all 15. In the remaining 74 men, gonadal function was studied after completion of chemotherapy (6 mo-8 yr). Semen was obtained from 49 men who had received six or more courses of MVPP. Forty-two were azoospermic and 5 of the remaining 7 had a sperm count below 1 million/ml. Decreased libido and sexual activity was common during treatment but in the majority of men these returned to normal after completion of chemotherapy. The median FSH and LH levels and the median increments in semen FSH and LH levels after LHRH administration were significantly elevated compared with an age-matched control group. The mean testosterone level of the patients was significantly lower than in controls suggesting Leydig cell damage but androgen replacement therapy was not indicated in any individual patient. No evidence of hyperprolactinemia as a result of MVPP therapy was found. These results suggest that sperm storage before chemotherapy represents the main possibility for these patients to have children after completing chemotherapy. Before starting chemotherapy, advice should be given to these patients concerning possible changes in sexual behavior during treatment and the very high incidence of permanent infertility following treatment. (Author abstract) (21 Refs)

6. MALIGNANT INTERSTITIAL CELL TUMOR OF THE TESTIS.

Chen KT, Spaulding RW, Flam MS, Brittin GM
Dept. Pathology, Fresno Community Hosp. and Medical Center, P.O. Box 1232, Fresno, CA, 93715
Cancer; 49(3):547-552 1982

A case of malignant interstitial cell tumor of the testis is reported and the literature is reviewed. Malignant interstitial cell tumors occur exclusively in adults. Gynecomastia was noted in 12% of the cases. Elevated plasma levels or increased urinary excretion of estrogen, 17-ketosteroid, or testosterone were demonstrated in 64% of the patients. Vessel invasion, which occurred in 74% of the patients, appears to be the only reliable histologic feature for predicting malignant behavior. There is no proved sensitivity to radiation or chemotherapeutic regimens in patients with disseminated tumor. Once the diagnosis of malignacy is histologically established, inguinal and retroperitoneal lymph node dissections, even in the absence of clinical evidence of metastasis, may be beneficial in providing early staging of the tumor and, perhaps, in preventing subsequent lymphatic spread. (Author abstract) (33 Refs)

7. PROLACTINOMAS, TESTOSTERONE-BINDING GLOBULIN, AND ANDROGEN METABOLISM.

Vermeulen A, Ando S, Verdonck L
Dept. Endocrinology-Hematology, Academic Hosp., Univ. Ghent, B-9000 Ghent, Belgium
J Clin Endocrinol Metab; 54(2):409-412 1982

To study the mechanism by which PRL might influence the metabolism of androgens, the testosterone-binding capacity of testosterone-estradiol-binding globulin (TeBG) as well as the free testosterone (T) fraction were determined in patients with prolactinoma. In untreated patients with prolactinoma, the TeBG capacity was decreased and the free T fraction was increased. Whereas in males, the plasma (free) T concentration was decreased, the apparent free T concentration was increased in women. The increased free T fraction had as a consequence an increase in MCRs of both T and 5alpha-androstan-17beta-ol-3-one; the MCR of androstenedione was normal. It is concluded that besides the well known factors, such as estrogens, androgens, and thyroid hormones, PRL appears, at least in prolactinoma patients, influence the TeBG level. (Author abstract) (26 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

8. ESTROGEN AND PROGESTERONE RECEPTORS AND RESPONSE TO AN ANTIESTROGEN OF POST-MENOPAUSAL ENDOMETRIAL CARCINOMA AND METASTATIC BREAST CANCER.

Baulieu EE, Mortel R, Levy C, Namer M, Robel P
Lab. Hormones, 94270 Bicetre, France
Excerpta Med Int Congr Ser; 551:234-245 1981

The effects of tamoxifen (TAM) on estradiol (ER) and progesterone receptor (PR) sites were measured in endometrial cancers and in skin metastases of breast cancers. In a group of 43 postmenopausal women with endometrial carcinoma, two biopsies from each were studied: at time of referral and during surgery or just prior to radiotherapy. Fifteen patients received TAM 40 mg/day po for 5-7 days after the first biopsy and the second biopsy was performed 12-18 hr after the last dose. Ten patients ingested 10 mg TAM 8 and 4 hr prior to the second biopsy. Total ER concentration (cytosol + nuclear) in tumors was similar to that in late proliferative phase of normal endometrium. Values for PR concentration were low and comparable to those found in the secretory phase of the normal menstrual cycle. No hormonal correlations of receptors was found. Where TAM immediately preceded biopsy, the ratio of cytoplasmic to nuclear receptor shifted in favor of nuclear receptors. In patients treated with TAM 12-18 hr before biopsy, PR sites increased in all but four samples, while in patients treated immediately before biopsy, no increase in PR was observed. TAM did not influence levels of ornithine decarboxylase or estradiol dehydrogenase. In a somewhat similar study in 21 women with advanced metastatic breast cancer, ER and PR were absent or low in 9; in 10/12 of the ER positive cases, only 2 were PR negative. There was a significant positive correlation between ER and PR in untreated tumors. After TAM administration, available ER sites were greatly decreased. No PR receptor change was observed where ER was less than 20 femtomole/mg cytosol protein. Among the remaining cases, 7/12 showed an increase of PR of greater than 100 femtomole/mg cytosol protein. (35 Refs)

9. PREDICTING TREATMENT RESPONSE IN BREAST CANCER USING URINARY DISCRIMINANT RATIO AND RECEPTOR ASSAY.

Holdaway IM, Skinner SJ
Dept. Endocrinology, Auckland Hosp., Auckland 1, New Zealand
Eur J Cancer Clin Oncol; 17(12):1295-1300 1981

The ratio of urinary 11-desoxy-17-oxo steroids to urinary corticosteroids (discriminant ratio, DR) was compared with levels of tumor estrogen (ER) and progesterone (PR) receptor in 169 patients with early breast cancer. Approximately 205 of patients had significant levels in all three tests and 20% were negative by all three assays. However, patient status by ER and DR assay was in disagreement in 50% of cases. Retrospective analysis of 78 treatment courses of endocrine therapy in patients with disseminated breast cancer showed that out of the three predictive tests only ER assays reliably distinguished responding from non-responding patients. The same result was observed in a subgroup of 20 patients undergoing adrenal suppression with aminoglutethimide. When tests were combined in pairs, no combination, including either ER and PR or ER and DR, showed improved discrimination between responding and nonresponding patients compared to that seen with ER alone.

No predictive assay or combination of assays could usefully distinguish patients with a high likelihood of response to endocrine therapy. (Author abstract) (13 Refs)

10. DETERMINATION OF ESTROGEN RECEPTOR IN HUMAN COLON CANCER TISSUE WITH LABELED FLUORESCENCE ESTRADIOL (FLUORESCEIN ISOTHIOCYANATE).

Zhu N, Cai X, Wu L
Dept. Cancer Res., Second Hosp., Zhejiang Medical Univ., Hangzhou, People's Republic of China
Chin Med J [Engl]; 94(9):607-610 1981

Labeled fluorescence estradiol was used for determination of estrogen receptors (ER) in 33 specimens of colonic cancer. Ten specimens were ER positive. Of 10 specimens, 8 had histology of adenocarcinoma and 2 had histology of mucoadenocarcinoma. (10 Refs)

11. CYCLIC AMP-BINDING PROTEIN AND ESTROGEN RECEPTOR: ANTAGONISM DURING NUCLEAR TRANSLOCATION IN A HORMONE-DEPENDENT MAMMARY TUMOR.

Bodwin JS, Hirayama PH, Cho-Chung YS
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
Biochem Biophys Res Commun; 103(4):1349-1355 1981

Mutual inhibition of translocations from the cytoplasm to the nucleus by estrogen receptor (ER) and cyclic AMP-binding protein was examined in a cell-free system of mammary tumors. Incubation of nuclei from hormone-dependent MTW9 rat mammary tumors with cytosol activated by 5 nano (n)M 17beta-estradiol resulted in a 4-fold increase in nuclear estrogen binding activity over the control nuclei. The presence of 100 nM cyclic AMP (cAMP) in the activated cytosol inhibited nuclear uptake of ER by 50%. Incubation of the nuclei with cytosol activated by 100 nM cAMP increased nuclear cAMP binding and cAMP-dependent protein kinase activity 4-fold. The presence of 5 nM 17beta-estradiol in the activated cytosol inhibited the nuclear cAMP binding and the protein kinase activity by 50%. No competition was found between estrogen and cAMP for each other's cytoplasmic binding proteins or the nuclear acceptor sites. Data suggest that a mutual antagonism exists between the cAMP-binding protein and ER during their nuclear translocation; the mutual antagonism was dependent on concentrations of the ligands in the activated cytosol. Activated glucocorticoid receptors did not influence the nuclear uptake of either ER or cAMP-binding proteins. Studies on the structural conformation of cAMP- and estrogen binding proteins under controlled conditions of phosphorylation and dephosphorylation may elucidate the mechanism of antagonism between the receptors. (15 Refs)

12. ACTIVATION AND PARTIAL PROTEOLYSIS OF VARIANT GLUCOCORTICOID RECEPTORS, STUDIED BY TWO-PHASE PARTITIONING.

Andreasen PA, Gehring U
Inst. Experimental Hormonforskning, Kobenhavns Universitet, Norre Alle 71, DK-2100 Kobenhavn, Denmark
Eur J Biochem; 120(3):443-449 1981

In cultured lines of mouse lymphoma cells, resistance to glucocorticoids is frequently associated with the occurrence of glucocorticoid receptors with an abnormally low affinity (nt-) or an abnormally high affinity (nti) for nuclei and DNA. We have investigated whether the abnormal affinities for DNA are correlated with alterations in charge and surface properties of the receptors, that would be revealed through the partition coefficient in aqueous dextran/poly(ethylene glycol) two-phase systems. We have found that none of the receptor variants is defective in the activation step per se, and that only the nti receptors are abnormal in partition properties. Partial proteolysis of wild-type and nt- receptors and alpha-chymotrypsin produces forms which are indistinguishable from the nti receptors with respect to partition coefficients. Upon alpha-chymotrypsin treatment the wild-type receptors attain DNA-binding properties identical to those of the nti receptors, while the nt- receptors, in spite of some increase in DNA affinity, still bind less firmly to DNA than the alpha-chymotrypsin-treated wild-type receptors. Alpha-chymotrypsin treatment of the various receptors types also produces an increase in the binding to dextran sulfate, but the dextran sulfate affinity is higher and varies less between different receptor types than the DNA affinity. Trypsin-treated receptors were found to be devoid of affinity for DNA and dextran sulfate. We conclude that the increased DNA affinity of the nti receptors is due to a gross change in the structure of the receptors, while the decreased DNA affinity of the nti receptors is caused by more subtle alterations in the polyanion binding domain of the receptors. (Author abstract) (17 Refs)

13. FLUORESCENCE-MICROSCOPIC DEMONSTRATION OF ESTROGEN- AND PROGESTERONE-RECEPTORS IN MAMMARY TUMORS OF THE DOG.

Elling H, Staimer S
Institut fur Tierpathologie, Ludwig-Maximilians-Universitat Munchen, Veterinarstr. 13, D-8000 Munchen 22, W. Germany
Berl Muench Tieraerztl Wochenschr; 94(23):468-471 1981

Tissue sections from eight canine mammary tumors were examined by fluorescence microscope (FM) to determine estrogen- and progesterone-receptor status. Tissue samples were frozen in liquid nitrogen immediately after surgical removal. Serial sections were prepared and stained with hematoxylin and eosin, estradiol conjugate, or progesterone conjugate. Cells were graded as nonspecific, weakly, moderately, or strongly fluorescent; nuclear and cytoplasmic staining were not differentiated. Estrogen- and progesterone-conjugates accumulated in the cell cytoplasm and, to a smaller degree, in the nucleus. In each tumor examined, different areas showed different degrees of fluorescence. Fluorescence was found only in tumor cells; leukocytes, blood vessels, and adjacent connective tissue showed no fluorescence. Estrogen and progesterone receptors were found in both epithelial and myoepithelial components of tumors. Determination of receptor status by FM had the advantages over radioimmunoassay of reduced cost and equipment requirements and direct counting of fluorescent cells. Disadvantages included subjective, rather than objective grading and variation in fluorescence with the thickness of tissue sections. Results indicate that canine mammary tumors are not strictly receptor-positive or negative but consist of heterogeneous cell populations. (18 Refs) (In GER)

14. DEFECTIVE STEROID RECEPTORS IN A GLUCOCORTICOID RESISTANT CLONE OF A HUMAN LEUKEMIC CELL LINE.

Harmon JM, Schmidt TJ, Thompson EB
Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD, 20205
Adv Exp Med Biol; 138:301-313 1982

Several glucocorticoid resistant mutants derived from the steroid sensitive human leukemic cell line CEM-C7 were isolated, characterized, and studied. The mutants contain receptors capable of binding glucocorticoids. Results indicate that mere presence of steroid binding activity, even in cells or tissues which generally express steroid regulated functions, does not guarantee the existence of a functional, steroid responsive, pathway. More detailed analyses of glucocorticoid receptors from clinical material is required to establish a relationship between receptors and clinical response. (30 Refs)

15. GLUCOCORTICOID RECEPTOR AND IN VITRO SENSITIVITY TO STEROID HORMONES IN HUMAN LYMPHOPROLIFERATIVE DISEASES AND MYELOID LEUKEMIA.

Nanni P, Nicoletti G, Prodi G, Galli MC, De Giovanni C, Grilli S, Lollini PL, Gobbi M, Cavo M, Tura S
Istituto di Cancerologia, Universita di Bologna, via S. Giacomo 14, 40126 Bologna, Italy
Cancer; 49(4):623-632 1982

The glucocorticoid receptor (GR) quantitation by a whole-cell assay and/or cytosol technique and the in vitro sensitivity to steroids have been assessed in peripheral blood cells from normal donors and patients with chronic lymphatic leukemia (CLL), acute lymphoblastic leukemia (ALL), lymphosarcoma cell leukemia (LSCL), acute nonlymphatic leukemia (ANLL), and chronic myeloid leukemia (CML). Within the lymphoproliferative diseases, ALL cells exhibited the highest GR concentration (regardless of the method used) and the highest in vitro inhibition of spontaneous [3H]thymidine ([3H]TdR) uptake by glucocorticoids. A significant relationship between GR concentration (whole-cell assay) and in vitro sensitivity to dexamethasone was also found. On the contrary, CLL cells presented the highest sensitivity to glucocorticoids in PHA-stimulated cell cultures. Cells from the only two ALL patients who did not undergo a remission after glucocorticoid-inclusive chemotherapy had both the lowest in vitro sensitivity to dexamethasone and the lowest GR concentration with whole-cell assay. Concerning myeloid leukemia, ANLL patients had GR concentrations slightly higher than those found in the ALL group but exhibited the lowest degree of inhibition of spontaneous [3H]TdR uptake by dexamethasone (stimulatory effects occurred in some cases). CML cells exhibited an inhibition degree by in vitro glucocorticoids significantly higher than that of ANLL cells but not different from that of lymphoproliferative diseases. No clear relationship among GR pattern, in vitro cell sensitivity to glucocorticoids, and clinicohematologic parameters was observed in myeloid leukemia-bearing patients. (Author abstract) (38 Refs)

16. STEROID RECEPTOR PROTEINS IN HUMAN MENINGIOMAS.

Tilzer LL, Plapp FV, Evans JP, Stone D, Alward K
Clinical Lab., Kansas Univ. Medical Center, Coll. Health Sciences and Hosp., 39th and Rainbow Blvd., Kansas City, KS, 66103
Cancer; 49(4):633-636 1982

Steroid receptor assays play an important role in determining the efficiency of endocrine therapy for patients with breast cancer. Other tumors could also be hormonally dependent and patients with these tumors might also benefit from endocrine manipulation. Thus, patients with meningiomas were tested for the presence or absence of estrogen and progesterone receptors. The results showed that a majority of meningiomas lacked estrogen receptors but contained large amounts of progesterone receptor. Therefore, it should be possible to use antiprogestin therapy in cases where complete surgical resection of meningiomas is not possible. (Author abstract) (10 Refs)

17. LACK OF ASSOCIATION BETWEEN WEIGHT AND OESTROGEN RECEPTORS IN WOMEN WITH BREAST CANCER.

Mason B, Holdaway IM, Yee L, Kay RG

Dept. Surgery, Auckland Hosp., Park Road, Auckland 1, New Zealand

J Surg Oncol; 19(1):62-64 1982

Evidence for a relationship between body weight and tumor estrogen receptor (ER) level has been sought in women with newly diagnosed breast cancer. There was no significant correlation between body weight and tumor ER concentration, either over the whole of observed weight or when considering groups above or below a weight of 68 kg. Similarly, when women were subgrouped by prognostic variables such as nodal status, tumor size, or menopausal status, there was no significant relationship between ER level and body weight. These data suggest that observations linking breast cancer risk with increasing body weight cannot be explained by variations in ER level. (Author abstract) (10 Refs)

18. THE DETECTION OF GLUCOCORTICOID RECEPTORS IN BREAST CANCER BY IMMUNOCYTOCHEMICAL AND BIOCHEMICAL METHODS.

Ioannidis C, Papamichail M, Agnanti N, Garas J, Tsawdaroglou N, Sekeris CE

Hellenic Anticancer Inst., Athens, Greece

Int J Cancer; 29(2):147-152 1982

Glucocorticoid receptors have been detected in 90 human breast tumors and tumor-like conditions by the immunoperoxidase method using a specific antibody against the glucocorticoid receptor isolated from rat thymocytes. In some of the specimens the [3H]-dexamethasone binding assay was also performed and the results obtained were compared with those of the immunoperoxidase method. When the biochemical method was used, no strict correlation between the degree of binding of [3H]-dexamethasone and malignancy on the basis of histological findings could be demonstrated. In contrast, the immunoperoxidase method was in full agreement with the histological type of the tumor. Thus, nearly all malignant breast tumors (carcinomas) were positive by the immunoperoxidase method to a varying degree. Most of the examined benign tumor-like conditions (fibrocystic disease) were found to be negative. Intermediate situations, such as atypical duct or lobular hyperplasia, papillomatosis etc, were mostly positive. These findings suggest that the immunoperoxidase method, apart from its usefulness for the detection of glucocorticoid receptors in breast tissue, may be used as an early biological marker to detect early conversion of normal to hyperplastic tissue and/or malignancy of the mammary gland. (Author abstract) (14 Refs)

19. POSTOPERATIVE TREATMENT OF MAMMARY CARCINOMA WITH SPECIAL CONSIDERATION OF HORMONE RECEPTORS AND HORMONE THERAPY.

Salzer H
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Gynaekol Rundsch; 21(Suppl2):23-27 1981

The significance of hormone receptors (HR) and hormone therapy (HT) in the treatment of mammary carcinoma is reviewed. HT affects tumor cells by blockading HR with antiestrogens, gestagen, or androgens or by competing for HR by administration of high doses of estrogens. HT produces a response in approx 30% of breast cancers (50-65% of HR-positive cases and 8-12% of HR-negative cases). Response rate increases in proportion to the cellular concentration of HR: An HR concentration of 100 femtomoles HR/mg cytosol protein corresponds to a response rate of greater than 80%. The greatest response rate is found among patients whose tumors are positive for both estrogen- and progesterone-receptors. Approx 33% of HR-positive cases do not respond to HT, possibly because of defective receptor molecules. No correlation has been established between HR status and response to cytostatic therapy. HT is indicated for all HR-positive breast cancers; in premenopausal and early menopausal patients HT should include ovariectomy. Adrenalectomy and hypophysectomy should be used as a last resort. The most common additive HT uses Tamoxifen. Early results suggest equal or better results, including a reduction of side effects, with medroxyprogesterone acetate. Overall results suggest that HT can reduce the rate of recurrence of breast cancer. (10 Refs) (In GER)

20. THE INCIDENCE OF POSITIVE OESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER OF GREEK WOMEN.

Vassilaros S, Adamopoulos DA, Papadiamantis J, Dessypris A, Kapolla N
Breast and Endocrine Clinic, M. Eliadi' Hosp., 2, E. Venizelou Square, Athens 601, Greece

Anticancer Res; 1(4):195-197 1981

Estrogen and progesterone receptors (ER and PR, respectively) were determined in breast tumors from 80 Greek women (23-72 yr old). Of the patients positive for both ER and PR, 15 were assayed for prolactin (PRL), thyroid stimulating hormone (TSH), and human chorionic gonadotropin (HCG beta subunit). ER assays were positive in 84.6% of premenopausal and 85.4% of postmenopausal women. PR assays were positive in 71.8% of premenopausal and 58.5% of postmenopausal women. In premenopausal women, both receptors were positive in 69.2%, ER was positive and PR negative in 15.4%, ER was negative and PR positive in 2.6%, and both were negative in 12.8%. In the postmenopausal group, 51.2% were positive for both ER and PR, 34.2% were ER positive and PR negative, and 14.6% were negative for both. The mean ratio of PR to ER concentration in the premenopausal group was 7.6 compared with 1.7 in the postmenopausal group. In receptor positive patients, PRL and TSH concentrations were similar to those of patients with cystic disease and fell within the normal range of values. HCG was not detected in any patients or controls. These data demonstrate that the frequency of positive ER and PR in Greek women with breast cancer is similar to that of other Western populations. (17 Refs)

21. PROGNOSTIC VALUE OF THE ESTROGEN RECEPTOR LEVEL IN PATHOLOGIC STAGE I AND II ADENOCARCINOMA OF THE BREAST.

Shapiro CM, Schifeling D, Bitran JD, Desser RK, Rochman H, Michel A, Shapiro R, Evans R, Kozloff MF, Recant W, Billings AA
(c/o Bitran) Div. Hematology/Oncology, Michael Reese Hosp. and Medical Center, 29th St. and Ellis Ave., Chicago, IL, 60616

J Surg Oncol; 19(2):119-121 1982

The relationship between estrogen receptor levels and recurrence of breast cancer was examined in 302 patients with adenocarcinoma of the breast, pathologic Stage (PS) I and II. All 117 patients with PS II adenocarcinoma of the breast received adjunctive chemotherapy. In this series, there was no association between the estrogen receptor level and recurrence in either the 185 patients with PS I adenocarcinoma of the breast or the 117 patients with PS II adenocarcinoma of the breast. The most important prognostic variable was the presence or absence of axillary metastases. (Author abstract) (13 Refs)

22. THE ROLE OF ESTROGEN RECEPTOR STATUS IN PREDICTING THE RESPONSE OF CARCINOMA OF THE BREAST TO ADJUVANT CHEMOTHERAPY.

Stephens RB, Abeloff MD, Mellits ED, Baker RR
Dept. Surgery, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD

Surg Gynecol Obstet; 154(2):200-204 1982

This study was undertaken to determine if there was any correlation between the estrogen receptor status and the response of patients with operable carcinoma of the breast to adjuvant chemotherapy. Seventy-seven patients with metastases to the axillary lymph nodes who were receiving adjuvant chemotherapy following a modified radical mastectomy were studied. During the period of study, 12 of 34 estrogen receptor-positive tumors recurred, with a mean disease-free interval of 17.8 mo, and 19 of 43 estrogen receptor-negative tumors recurred, with a disease-free interval of 15.2 mo. Statistical analysis of recurrence at 2 yr showed no difference between these two groups. Only one patient of 18 in the premenopausal group of women with estrogen receptor-positive tumors, however, had a recurrence compared with 11 of 24 patients with estrogen receptor-negative tumors. This difference was highly statistically significant (p greater than 0.0005). We have concluded that the estrogen receptor status is not a reliable indicator of response to adjuvant chemotherapy for all patients. Our data do indicate a positive correlation between response to adjuvant chemotherapy and estrogen receptor status in the premenopausal group of patients and suggest that adjuvant chemotherapy in the premenopausal group of patients may be exerting some of its effect by ovarian suppression rather than by a solely cytotoxic effect on cancer cells of the breast. (Author abstract) (8 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

23. COMPARATIVE STUDY OF ESCHERICHIA COLI ENDOTOXIN, HYDROCORTISONE AND BELJANSKI LEUKOCYTE RESTORER ACTIVITY IN CYCLOPHOSPHAMIDE-TREATED RABBITS.

Plawecki M, Beljanski M
Faculte de Pharmacie, Service de Pharacohynamie, Chatenay Malabry 92290, France
Proc Soc Exp Biol Med; 168(3):408-413 1981

Leukopoietic activities in rabbits in the presence of Beljanski leukocyte restorer (BLR), endotoxin, or hydrocortisone were compared. The concentration of bacterial endotoxin which induced a significant leukocyte response in cyclophosphamide (CP)-treated rabbits was about 1.7 ug/kg. Maximum increase in leukocyte count occurred before the 24th hr following endotoxin injection. Compared to endotoxin, BLR induced increased numbers of both white blood cell types, reaching a maximum 48 hr after injection. These results indicated that the kinetics of granulocytes and lymphocytes induced by BLR in CP-treated rabbits differed markedly from those induced under identical conditions using bacterial endotoxin. In contrast to results obtained with endotoxin, no tolerance was observed with BLR even after multiple injections. Only BLR and not endotoxin was found capable of sustaining leukopoiesis in tolerant rabbits initially given a mixture of the two compounds. Results indicate that BLR can be distinguished from endotoxin or corticoid as a new class of hematopoietic promoters. (19 Refs)

24. NORMAL SISTER-CHROMATID EXCHANGES IN ORAL CONTRACEPTIVE USERS.

Husum B, Wulf HC, Niebuhr E
Dept. Anaesthesia, Rigshospitalet, Copenhagen, Denmark
Mutat Res; 103(2):161-164 1982

A group (A) of 63 women (15-42 yr old; av 22.3) who used no medication whatsoever was compared with a second group (B) of 52 women (16-43 yr old; av 26.3) who used oral contraceptives (OC; combinations of progestins and estrogens) with respect to the effect of cigarette smoking on sister chromatid exchanges (SCE) in peripheral lymphocytes. Mean numbers of SCE/cell ranged from 8.42-9.52 for group A, and 8.54-10.36 for group B, over a range of cigarette use of 0-greater than 20/day. The total number of SCE in 30 metaphases of each woman was transformed from an assumed Poisson distribution to a normal distribution, and a linear regression and Bartlett's test were performed which gave independent estimates of basic variance summed as 4.43 for group A and5.97 for group B. It was concluded that use of OC does not influence SCE in lymphocytes in either smoking or nonsmoking women. (8 Refs)

25. EFFECTS OF GLUCOCORTICOID HORMONES ON CELL PROLIFERATION IN DIMETHYLHYDRAZINE-INDUCED TUMOURS IN RAT COLON.

Tutton PJ, Barkla DH
Dept. Anatomy, Monash Univ., Clayton, Victoria, 3168, Australia
Virchows Arch [Cell Pathol]; 38(2):247-251 1981

Adrenocortical hormones have previously been shown to influence cell proliferation in many tissues. In this report, their influence on cell proliferation in the colonic crypt epithelium and in colonic adenocarcinomata is compared. Colonic tumor cell proliferation was found to be retarded following adrenalectomy and this retardation was reversible by administration of hydrocortisone, or by administration of synthetic steroids with predominantly glucocorticoid activity. Tumor cell proliferation in adrenalectomized rats was not promoted by the mineralocorticoid hormone aldosterone. Neither adrenalectomy, nor adrenocortical hormone treatment, significantly influenced colonic crypt cell proliferation. (Author abstract) (21 Refs)

26. EFFECT OF ESTRADIOL ON THE ULTRASTRUCTURE OF THE MCF7 HUMAN BREAST CANCER CELLS IN CULTURE.

Vic P, Vignon F, Derocq D, Rochefort H
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Cancer Res; 42(2):667-673 1982

We have analyzed the effect of estradiol and of two classes of antiestrogens on the morphology of the MCF7 human breast cancer cell line by scanning and transmission electron microscopy. Estradiol progressively increased the number and the length of microvilli at the cell surface. The density of the microvilli network increased between 2 and 11 days of estrogen treatment, while the cells became more globular and less tightly attached to the surface of the dish. Estradiol also progressively transformed cells into secretory cells containing, at Day 2, large, clear mitochondria and, at Day 4, rough endoplasmic reticulum and Golgi complexes. At Day 6, secretory granules (diameter, 0.2 um), which mainly contained glycoproteins, were first observed in the cytoplasm. By Day 8, they were concentrated at the cell membrane and being liberated into the medium. Larger granules (diameter, 0.8 um), which probably contained lipids, were observed later (Day 11). Cell cultures in 10% fetal calf serum not treated by charcoal contained secretory granules. The modifications were induced by physiological concentrations of estradiol but not 5alpha-dihydrotestosterone. Progesterone (10 nM for 8 days) completely inhibited the effect of estradiol on the microvilli and secretory activity. Tamoxifen or hydroxytamoxifen did not induce secretory activity but did alter the cell morphology compared to control cells. The effects of estradiol were observed in other estrogen receptor-positive breast cancer cell lines (ZR 75-1, T 47 D) but not in an estrogen receptor-negative cell line (BT 20). This morphological evidence that estrogens modify the cell surface of breast cancer cells in culture and transform them into 'secretory cells' complements evidence that they induce the release of a glycoprotein with a mol wt of approx 50,000 into the culture medium. (The mol wt was found first to be 46,000. It seems to be closer to 52,000 in a 10% polyacrylamide gel and by using the NEN-labeled proteins as mol wt markers.) (Author abstract) (30 Refs)

27. SELECTIVE INHIBITION BY SODIUM BUTYRATE OF GLUCOCORTICOID-INDUCED TYROSINE AMINOTRANSFERASE SYNTHESIS IN HEPATOMA TISSUE-CULTURED CELLS.

Tichonicky L, Santana-Calderon MA, Defer N, Giesen EM, Beck G, Kruh J
Institut de Pathologie et Biologie Cellulaire et Moleculaire, Centre Hospitalier Universitaire Cochin-Port Royal, 24 Rue du Faubourg-Saint-Jacques, F-75014 Paris, France
Eur J Biochem; 120(3):427-433 1981

Sodium butyrate at a 5 mM concentration prevents the induction of tyrosine aminotransferase in hepatoma culture cells, without affecting the basal level of the enzyme. This effect is reversible immediately after the removal of butyrate, or after a lag, if butyrate was present for more than 2 hr. Neither the amount of cellular RNA nor the rate of total RNA synthesis were affected by sodium butyrate. Furthermore butyrate does not inhibit protein synthesis: [35S]methionine incorporation into proteins, measured in a reticulocyte lysate system, shows no significant difference between the translation capacity of the RNAs from butyrate-treated cells and from dexamethasone-induced or uninduced cells. Nevertheless, when tyrosine aminotransferase was isolated from the translation products by its specific antiserum and analyzed by gel electrophoresis, we observed that the amount of the enzyme synthesized in the presence of RNAs from dexamethasone/butyrate-treated cells was strongly diminished relative to that synthesized in the presence of RNA from dexamethasone-induced cells. These experiments indicate that the treatment of the cells with butyrate decreases the activity of the specific messenger RNA for tyrosine aminotransferase to a level close to the basal level. Butyrate does not prevent the penetration of the hormone and has a limited effect on the translocation of the glucocorticoid-receptor complex to the nucleus. We therefore conclude that the effect of sodium butyrate might be inherent either to an impairment of an early step of the hormone-chromatin interaction or to an alteration of the transcription process of some specific genes. The rapidity and the complete reversibility of the effects of butyrate suggest that it does not irreversibly alter the structures which are the targets of its action. (Author abstract) (51 Refs)

28. REGULATION OF PITUITARY GROWTH AND PROLACTIN GENE EXPRESSION BY ESTROGEN.

Lieberman ME, Maurer RA, Claude P, Wiklund J, Wertz N, Gorski J
Dept. Biochemistry and Animal Science, Univ. Wisconsin, Madison, WI, 53706
Adv Exp Med Biol; 138:151-163 1982

The site of estrogen action and the molecular events involved in the regulation of prolactin synthesis were studied using monolayer cultures of dispersed rat pituitary cells. Primary cultures of rat pituitary cells respond to estradiol by increased incorporation of precursors into prolactin. Time and magnitude of response are in agreement with that observed under in vivo conditions suggesting that estrogen exerts its effect through a direct action on the pituitary gland. Chronic treatment with diethylstilbestrol caused sustained proliferation of pituitary tumors in the Fisher 344 rat, but not in the Holtzman rat. (33 Refs)

29. AXC RAT PROSTATIC ADENOCARCINOMA: CHARACTERIZATION OF CELLS IN CULTURE.

Shain SA, Boesel RW, Kalter SS, Heberling RL
Southwest Foundation for Res. and Education, San Antonio, TX, 78284
Adv Exp Med Biol; 138:337-351 1982

Some of the biochemical properties of the LSC-AXC rat prostate cancer cell line which suggest that these cells are highly androgen responsive were studied. Response of androgen and prolactin receptors and L-ornithine decarboxylase in LSC-AXC prostatic cancer cells and tumors to androgen ablation is indistinguishable from that of ventral prostate. LSC-AXC prostatic tumors retain levels of secretory acid phosphatase comparable to those of ventral prostate of aged AXC rats. (22 Refs)

30. DEFECTIVE CENTRAL NERVOUS SYSTEM DOPAMINERGIC FUNCTION IN RATS WITH ESTROGEN-INDUCED PITUITARY TUMORS, AS ASSESSED BY PLASMA PROLACTIN CONCENTRATIONS.

Casanueva F, Cocchi D, Locatelli V, Flauto C, Zambotti F, Bestetti G, Rossi GL, Muller E
(c/o Muller) Dept. Pharmacology, Univ. Milan, Via Vanvitelli, 32, 20129 Milan, Italy
Endocrinology; 110(2):590-599 1982

Mature cycling female rats were each injected at 3-wk intervals with 2 mg estradiol valerate (EV) in sesame oil. Controls received an equivalent volume of sesame oil. The administration of EV induced, at first, hyperplasia and then, 10 wk after the first EV injection, adenomatous changes in the pituitary gland. Concurrently, there was a striking rise in plasma PRL concentrations, which reached values of about 2 ug/ml at 25 wk. Acute administration of nomifensine (NOM), an indirectly acting dopamine (DA) agonist, to EV-injected rats suppressed baseline PRL levels at 1 wk, but failed to significantly decrease PRL levels at 4, 7, 10, and 25 wk. Unlike NOM, bromocriptine, a direct DA agonist, strikingly reduced baseline PRL levels in EV-injected rats 1, 10, and 25 wk after the first EV injection. The administration of domperidone (DOM), a potent blocker of DA receptors, inconsistently increased plasma PRL at 1 wk and was ineffective at the following time intervals. Light and electron microscopic examinations of the hypothalamus revealed the existence in EV-injected rats of pathological changes in the arcuate nucleus region. In addition, measurement of DA in the median eminence of diluent- and EV-injected rats showed in the latter the presence of progressively reduced DA concentrations. These data suggest that rats with primary estrogen-induced PRL-secreting tumors have a defect in CNS-DA neurotransmission, a condition which has been postulated to also occur in human subjects bearing a prolactinoma. (43 Refs)

31. INDUCER-MEDIATED COMMITMENT OF MURINE ERYTHROLEUKEMIA CELLS TO DIFFERENTIATION: A MULTISTEP PROCESS.

Chen ZX, Banks J, Rifkind RA, Marks PA
Soochow Medical Coll., Soochow, People's Republic of China
Proc Natl Acad Sci USA; 79(2):471-475 1982

There are a number of agents which, when added to cultures of murine erythroleukemia cells (MELC), markedly increase the probability of commitment to express the characteristics of terminal erythroid differentiation, including loss of proliferative capacity and increased accumulation of globin mRNA and hemoglobin. Some characteristics of inducer-mediated commitment of MELC to terminal erythroid differentiation were examined by determining the effects of dexamethasone (an inhibitor of inducer-mediated MELC differentiation) and of hemin (an inducer of globin mRNA accumulation). Previously, it was shown that exposure of MELC to hexamethylene-bisacetamide (HMBA) leads to commitment, detectable within 12 hr. MELC cultured with both HMBA and dexamethasone do not express commitment. MELC transferred from culture with HMBA and dexamethasone to cloning medium without these agents express commitment to terminal erythroid differentiation, indicating that MELC retain a 'memory' for some early HMBA-mediated changes leading to commitment which occur even in the presence of the inhibitory steroid. The kinetics of commitment in experiments in which exposure to HMBA is interrupted, or dexamethasone is added to the culture with HMBA, suggest that there is a rate-limiting step early in the commitment process. The memory for this step persists for more than one cell cycle. Addition of hemin to cultures with HMBA and dexamethasone initiates accumulation of globin mRNA but does not reverse the steroid-mediated inhibition of terminal cell division (that is, the cells retain their proliferative capacity). Inducer-mediated MELC commitment is associated with accumulation of the chromatin protein IP25; dexamethasone does not inhibit this accumulation. Accumulation of IP25 may be inducer-related, but it is not sufficient to cause expression of terminal erythroid differentiation. (Author abstract) (49 Refs)

32. ESTROGEN REGULATION OF GROWTH AND SPECIFIC PROTEIN SYNTHESIS IN HUMAN BREAST CAN CER CELLS IN TISSUE CULTURE.

Edwards DP, Adams DJ, McGuire WL
Dept. Medicine, Univ. Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX, 78284
Adv Exp Med Biol; 138:133-149 1982

New protein markers of estrogen action and dependence of progesterone receptors upon estrogen-stimulated cell growth were studied using MCF-7 human breast cancer cells in tissue culture. Results showed that estradiol stimulates DNA polymerase activity in normal target tissues. Progesterone receptor induction and estrogen-mediated cell division may involve separate control mechanisms. A specific 24,000 mol wt protein may be a marker of estrogen-stimulated growth of human breast tumor cells. (27 Refs)

33. THE EFFECT OF TESTOSTERONE TREATMENT ON THE ABILITY OF FEMALE RAT LIVER S9 TO ACTIVATE AFLATOXIN B1 AND 2-AMINOFLUORENE IN THE AMES/SALMONELLA SYSTEM.

Chernesky P, Jayaraj A, Richardson A
Dept. Chemistry, Illinois State Univ., Normal, IL, 61761
Mutat Res; 103(3-6):267-273 1982

The activation of aflatoxin B1 (AFB1) and 2-aminofluorene (2AF) by liver homogenates (S9) from untreated and testosterone-treated female Fischer F344 rats was compared using the Ames Salmonella (TA98)/microsome assay. Testosterone treatment resulted in a 93% increase in the ability of S9 to convert AFB1 to mutagenic compounds in the Ames test and a 43% increase in the similar activation of 2AF. (21 Refs)

34. REVERSAL OF THE PROMOTIONAL EFFECT OF 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE ON MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY GLUCOCORTICOIDS.

Rivedal E
Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer Lett; 15(2):105-113 1982

Effects of glucocorticoids and cholesterol on morphologic transformation by benzo(a)pyrene (BP) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in hamster embryo cells were studied. Cells exposed to BP (0.05 ug/ml) during the first 3 days of incubation (period 1) and then to TPA (0.05 ug/ml) during the last 3 days (period 2) had a transformation frequency of 10.2%. When present during period 2, hydrocortisone and dexamethasone strongly inhibited the formation of transformed colonies. Corticosterone had only a slight inhibitory activity and cortisone had no inhibitory activity when administered in concentrations up to 25 uM. Dexamethasone, the most potent glucocorticoid, reduced transformation frequency by greater than 50% at 0.25 nanoM and completely abolished transformation at 250 nanoM. Cholesterol (2.5 or 25 uM) increased transformation frequency. The glucocorticoids had no effect when present only during period 1. The fact that addition of dexamethasone (250 nanoM) reduced transformation frequency even when added 6 hr before staining suggested that glucocorticoids rapidly reverse the morphology of transformed colonies back to normal. (31 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

35. DEHYDROEPIANDROSTERONE: AN ANTI-OBESITY AND ANTI-CARCINOGENIC AGENT.

Schwartz AG, Hard GC, Pashko LL, Abou-Gharbia M, Swern D
Fels Res. Inst., Temple Univ., Philadelphia, PA, 19140
Nutr Cancer; 3(1):46-53 1981

Effects of long-term administration of dehydroepiandrosterone (DHEA) on female C3H-Avy/A (obese) and C3H-A/A (non-obese) mice were examined. DHEA treatment significantly inhibited wt gain in both strains of mice without suppressing food consumption. Food consumption of the DHEA-treated C3H-A/A mice was significantly greater than that of controls. DHEA significantly reduced the rate of breast cancer development. From 12 to 18 mo of age, the difference in breast cancer rates between controls and DHEA-treated C3H-A/A mice was significant. In the C3H-Avy/A mice, significant differences in breast cancer rates between controls and DHEA-treated mice were evident between 10 and 15 mo. The C3H-Avy/A control mice experienced a marked enhancement in rate of breast cancer development when compared to the C3H-A/A control group. A single ip injection of DHEA (15 mg/kg) inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulation of 3H-thymidine incorporation in mouse epidermis. DHEA also blocked the TPA stimulation of 3H-thymidine incorporation in a rat kidney epithelial cell line; the inhibition was reversed by culturing for 20 hr in medium without DHEA. The results suggest that DHEA has an anti-carcinogenic effect and may have pharmacologic value in cancer prevention. (29 Refs)

36. GYNECOLOGICAL PROBLEMS IN WOMAN PATIENTS ON DIALYSIS TREATMENT AND IN WOMEN FOLLOWING RENAL TRANSPLANTS.

Baltzer J, Kurzl R, Eigler J, Samtleben W, Castro LA, Land W, Gurland HJ, Segerer W, Kuhlmann H, Zander J
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Geburtshilfe Frauenheilkd; 41(11):759-764 1981

Women patients on permanent dialysis treatment or after transplants display on the whole an increased rate of malignomas; however, it has so far not been possible to assess the relevant incidence in a uniform manner. Hence, regular gynecological examination should be the rule in order to detect and treat carcinoma risk changes in the genital region. Within the framework of a special gynecological consultation for renal patients we found in 81 woman patients under dialysis treatment one patient with carcinoma of the cervix and one patient with corpus carcinoma. In two cases a cystic ovarian tumor was operated on. To date the 21 patients who had undergone renal transplant surgery did not show any malignant change in the genital region. Choice of contraceptives should rule out the intrauterine device because of the increased hazard of infection under immunosuppressive treatment. Ovulation inhibitors with higher estrogen doses represent an additional hypertensive risk. Treatment with low-dosage gestagens should produce the lowest rate of side effects. (Author abstract) (67 Refs) (In GER)

37. CHANGES IN THE GONADS OF FEMALE CHICK EMBRYOS UNDER THE ACTION OF TAMOXIFEN.

Salzgeber B, Reyss-Brion M, Baulieu EE
Institut d'embryologie du C.N.R.S., 49 bis, avenue de la Belle-Gabrielle, 94130 Nogent-sur-Marne, France
C R Acad Sci [III] (Paris); 293(2):133-138 1981

The effect of tamoxifen (0.2 mg in olive oil), deposited on the embryonic blastoderm or chorioallantoic membranes of chick embryos between days 3 and 7 of incubation, on the development of the gonads was studied in the embryos on days 16-19 of incubation; in other studies, the tamoxifen (1.5 mg) was injected directly into the yolk sac between days 1 and 8 of incubation, and the chicks were examined after birth. The tamoxifen-treated embryos showed no significant differences from controls in hatching rate or in mortality rate during the first 3 wk after hatching. The tamoxifen proved to be strongly antiestrogenic and had no estrogen effect. The ovaries showed dense medullas with numerous cords and reduced cortexes. The development of the left ovary was partially inhibited, and the right gonad was partially regressed and 'masculinized'. Normal regression of the mullerian ducts was seen in the tamoxifen-treated male embryos. The findings suggest the physiological interference of tamoxifen with normal development of female chick embryos. (9 Refs) (In FRE)

38. EFFECT OF AN ESTROGEN ANTAGONIST (TAMOXIFEN) ON THE INITIATION AND PROGRESSION OF GAMMA-IRRADIATION-INDUCED MAMMARY TUMORS IN FEMALE SPRAGUE-DAWLEY RATS.

Welsch CW, Goodrich-Smith M, Brown CK, Miglorie N, Clifton KH, Goodrich-Smith M, Brown CK, Miglorie N, Clifton KH
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Eur J Cancer Clin Oncol; 17(12):1255-1258 1981

One hundred and sixty-eight female Sprague-Dawley rats were divided among four groups (42 rats/group) and were irradiated with 400 rad [137Cs] gamma rays to the whole body when 59 days old. The estrogen antagonist tamoxifen was injected sc daily from 29-89 days of age (Series 1) or from 89-149 days of age (Series 2), prior to the onset of palpable mammary tumors. Two groups of rats were injected with the diluent and served as controls. All rats were palpated bi-weekly for mammary tumors and killed 37 wk after gamma-irradiation. The number of mammary carcinomas which developed in each group and their significance levels were: series 1, controls, 31; tamoxifen treated, 11, p less than 0.01; series 2, controls, 33; tamoxifen treated, 17, p less than 0.01. Tamoxifen treatment did not significantly influence the incidence of benign mammary tumors (fibroadenomas) nor the rate of body wt gain. Thus, the effective use of an estrogen antagonist for the prophylaxis of radiogenic mammary carcinomas has been demonstrated in this study. (Author abstract) (13 Refs)

39. AMINOGLUTETHIMIDE AS TREATMENT OF POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CARCINOMA.

Santen RJ, Worgul TJ, Lipton A, Harvey H, Boucher A, Samojlik E, Wells SA
Milton S. Hershey Medical Center, Hershey, PA, 17033
Ann Intern Med; 96(1):94-101 1982

Hormone-dependent breast carcinomas respond to deprivation of biologically active estrogens with objectively quantifiable tumor regression. Aminoglutethimide, a known inhibitor of steroid synthesis, is also a potent blocker of the aromatase enzyme and, thus, of estrogen production. We develop an effective regimen to inhibit estrogen production in postmenopausal women using aminoglutethimide and replacement glucocorticoid. One hundred forty-seven women initially received aminoglutethimide and replacement glucocorticoid as treatment of metastatic breast carcinoma. One hundred twenty-nine women are currently evaluable for assessment of clinical and hormonal responses. Thirty-seven percent of unselected women and 49% of estrogen receptor-positive patients experienced objective tumor regression. Responses occurred predominantly in soft tissue (47%) and bone (35%) and lasted 30 +-9.1 mo for complete and 14 +-1.5 mo for partial regressions. Plasma and urinary estrogen levels fell equally in responder versus nonresponder groups whereas androgen levels declined less in patients with progressive disease. (Author abstract) (67 Refs)

40. PROTECTION AGAINST ENDOMETRIAL CARCINOMA BY COMBINATION-PRODUCT ORAL CONTRACEPTIVES.

Hulka BS, Chambless LE, Kaufman DG, Fowler WC, Greenberg BG
Dept. Epidemiology, Sch. Public Health, Univ. North Carolina, Chapel Hill, NC, 27514
JAMA; 247(4):475-477 1982

Seventy-nine patients with endometrial carcinoma were compared with 203 control subjects regarding their use of combination-product oral contraceptives (OCs). Overall, 6.3% of patients and 15.3% of control subjects had used these products. The risk of endometrial cancer for users of OCs was less than half the risk of nonusers. Five yr or more of use reduced the risk to a third. Recent users were strongly protected, whereas discontinuation resulted in risks returning to those of nonusers. Furthermore, OCs with predominantly progestational effects or intermediate formulations produced greater protection than those with predominantly estrogens. This pattern of results is biologically consistent with a protective effect of combination-product OCs against endometrial carcinoma. (Author abstract) (13 Refs)

41. LACK OF EFFECT OF DIETARY FAT ON THE GROWTH AND ESTROGEN SENSITIVITY OF THE MT-W9B TRANSPLANTABLE MAMMARY TUMOR.

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Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Nutr Cancer; 3(1):27-34 1981

Effects of diets containing low (LF: 0.5%) or high (HF: 20%) fat on the growth and estrogen responsiveness of the MT-W9B mammary tumor in Wistar-Furth rats were studied. Tumor growth was not significantly affected by HF or LF diet. Tumor growth was also unaffected in either group by ovariectomy (OVx), sham OVx, or by OVx with estradiol supplementation. Dietary fat intake did not alter the sensitivity of the uterus to estrogen. Progesterone receptor (PR) levels were slightly elevated in tumors from sham-OVx rats fed a HF diet compared those fed a LF diet; this increase was not statistically significant. Responses of PR to OVx or to OVx with estrogen supplementation were not altered by dietary fat levels. PR levels were decreased in OVx rats to 16% and 14% of control levels in LF and HF groups, respectively, and increased 16-fold and 13-fold, respectively, in OVx rats given estradiol. In the same tumors, estrogen receptor levels were not significantly altered by either dietary or hormonal manipulation. PR levels were elevated in uteri from sham-OVx rats fed a HF diet compared to those fed a LF diet when expressed on a picomole/uterus basis, but this increase was not statistically significant when expressed on a per mg basis. Dietary fat did not appear to affect the response of uterine PR to estrogen manipulation. Dietary effects on estrogen receptors are described. The results suggested that dietary fat does not influence the sensitivity of normal or neoplastic tissue to estrogen action. (37 Refs)

42. ANTITUMOR ACTIVITY, TOXICITY AND DISPOSITION OF LS 1727, A NITROSO-CHLOROETHYL CARBAMATE OF 19-NORTESTOSTERONE, IN RATS AND MICE.

Gunnarsson PO, Ellman M, Fabiansson E, Gunnarsson K, Jensen G, Muntzing J
Res. Lab., AB Leo, Box 941, S-251 09 Helsingborg, Sweden
Acta Pharmacol Toxicol (Copenh); 49(4):290-297 1981

LS 1727, a nitroso-chloroethyl carbamate of 19-nortestosterone, given intraperitoneally had a high cytostatic activity against some experimental tumors. In vitro studies showed that the tested tumors differed in their ability to hydrolyze LS 1727. The hydrolytic capacity was related to the sensitivity to treatment with LS 1727. Distribution studies with double-labeled LS 1727 demonstrated that the chloroethyl-part of the molecule was retained in dimethylbenz(a)anthracene-induced mammary tumors in the rat. Our findings suggest that the antitumor activity of LS 1727 is exerted by alkylating metabolites released at hydrolysis of the compound. LS 1727 had no oral antitumor activity probably due to pre-systemic hydrolysis. When given intravenously, hydrolysis of LS 1727 in lungs caused severe pulmonary toxicity already at low doses. (Author abstract) (21 Refs)

43. TREATMENT OF UTERINE BODY CARCINOMA AND SIDE-EFFECTS IN THE VALDARNO ARETINO AREA.

Ragazzini G, Migliorini A, Nunci A
Divisione Ostetrico-Ginecologica, Ente Ospedaliero del Valdarno Aretino, Montevarchi (AR), Italy
Minerva Ginecol; 33(11):1067-1070 1981

Forty-two patients with endometrial carcinoma (EC) of the uterine body having the following age distribution: 30-39 yr old (1), 40-49 yr old (2), 50-59 yr ol (14), 60-69 yr old (19), 70-79 yr old (5), and 80-89 yr old (1), were histologically diagnosed. The findings were as follows: adenocarcinoma (38), adenoacanthoma (3), and epidermoid carcinoma (1). Twenty eight patients were in Stage I, 9 in Stage II, and only 1 patient was in Stage 0. Forty patients were at menopause. Other diagnosed diseases were as follows: diabetes (11), hypertension (13), and obesity (12). All three conditions were combined in 10 patients. Thirty-seven patients underwent total hysterectomy, bilateral adnexectomy, and resection of upper third of the vagina. In one case surgery was performed through vagina. All patients received the progesterone preparation Gestorone (200-400 mg/wk) up to 2 yr. No mortality occurred during or immediately after surgery. Seven patients died later, two hade metastases, five were living more than 3 yr, four more than 4 yr, and eight more than 5 yr. (9 Refs) (In ITA)

44. BENEFICIAL EFFECTS OF AN ANABOLIC STEROID DURING CYTOTOXIC CHEMOTHERAPY FOR METASTATIC CANCER.

Spiers AS, DeVita SF, Allar MJ, Richards S, Sedransk N
Div. Oncology, Albany Medical Coll., Albany, NY, 12208
J Med; 12(6):433-445 1981

To investigate the effects of concurrent administration of an anabolic steroid upon hematopoiesis and metabolism in patients with cancer who were receiving cytotoxic chemotherapy, a randomized trial was conducted. Thirty-three evaluable patients received intensive multiple-agent chemotherapy: 17 received in addition nandrolone decanoate ('Deca-Durabolin'), 200 mg intramuscularly each week. The nandrolone-treated patients showed significantly better maintenance of hemoglobin concentrations and body wt, and a highly significant reduction in number of blood transfusions. Improved survival in the androgen-treated patients did not achieve significance. There were no differences in neutrophil or platelet counts or in tolerance of cytotoxic drugs. Toxicity from nandrolone therapy was minimal. (Author abstract) (6 Refs)

45. TURISTERON: CLINICAL EXPERIENCE WITH A DEPOT ESTROGEN IN THE TREATMENT OF METASTATIC MAMMARY CARCINOMA.

Gurtler R, Tannenberger S, Bodek B, Morack G, Tannenberger S, Bodek B, Morack G
Zentralinstitut fur Krebsforschung der AdW, Lindenberger Weg 80, DDR-115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(2):129-139 1982

Sixty patients (54-86 yr old, av age 70 yr) in late menopause with metastatic mammary carcinoma were treated with the depot estrogen Turisteron. Forty-nine patients had undergone radical mastectomy; 2 had undergone simple mastectomy. Results in 51/60 patients were evaluable. Of these 51, 11 received 1 mg Turisteron/wk, po; 40 received 2 mg/wk. The lower dose was found to be unsatisfactory; a dose of 3 mg/wk was not tolerated well. Of the 40 patients receiving 2 mg/wk, 7.5% achieved complete remission with an av duration of 27 mo; 22.5% achieved partial remission with a 10 mo av duration, 10.0% showed clinical improvement, 32.5% showed tumor progress, 5.0% showed tumor stimulation, and 5.0% showed hypercalcemia. Results of therapy began to appear 4-6 wk after start of treatment. Turisteron was particularly effective against soft-tissue and lung metastases. Results indicate that Turisteron is suitable for treatment of metastatic mammary carcinoma during late menopause. Contraindications for treatment include cardiovascular disorders, liver damage, and hypercalcemia. Replacement of Turisteron therapy with cytostatic therapy if tumor stimulation occurs is recommended. (26 Refs) (In GER)

46. TREATMENT OF BONE METASTASES FROM BREAST CANCER.

Gottwald G, Szakolczai I
Radiologiai Klinika, Semmelweis Orvostudomanyi Egyetem, Budapest, Hungary
Orv Hetil; 122(45):2771-2775 1981

The treatment of 68 women (av age 59 yr, 30-79 yr old) with bone metastases of breast cancer is reported. Twenty-seven patients were in the premenopause, 10 at the climacterium and 31 in the menopause at the time of diagnosis of the bone metastases. At the time of surgery for breast cancer, 1 patient was in Stage I, 11 were in Stage II, III in Stage III, 7 in IV, and the stages of 35 patients were unknown. The symptom-free interval was 0-0.5 yr in 13 patients, 0.5-2 yr in 26, 2-4 yr in 17, 4-8 yr in 10, and more than 8 yr in 2. Four patients were symptom-free at the time of diagnosis of the bone metastasis, 62 had pains, 40 restricted mobility, 11 neurological symptoms, and 6 pathological fractures. Solitary bone metastases were found in 6 patients, multiple bone metastases in 62. Sixteen patients had only bone metastases, 52 had other metastases as well. The treatment consisted of radiotherapy in 15 cases, ovariectomy in 11, androgen or anabolic treatment in 26, antiestrogen treatment in 42, corticosteroid treatment in 16, progesterone or estrogen treatment in 4, cyclophosphamide + methotrexate + Ftorafur in 40, adriamycin + vincristine in 7 and of carmustine or dibromodulcitol in 9. Sixty-six patients responded to the treatment; their improvements lasted 14 mo, but objective remission was achieved in 15/68 patients only. The mean length of objective remission was 17 mo. Thirty-three patiens (2 with solitary and 31 with multiple bone metastases) died. Four patients with solitary and 31 with multiple bone metastases have been alive for at least 25 and 18 mo, respectively, after the diagnosis of the bone metastases. (19 Refs) (In HUN)

47. INHIBITION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE- AND URETHAN-INDUCED LUNG TUMOR FORMATION IN A/J MICE BY LONG-TERM TREATMENT WITH DEHYDROEPIANDROSTERONE.

Schwartz AG, Tannen RH
Fels Res. Inst. and Dept. Microbiology, Temple Univ. Medical Sch., Philadelphia, PA, 19140
Carcinogenesis; 2(12):1335-1337 1981

Long-term treatment with the adrenal steroid dehydroepiandrosterone reduces weight gain without suppressing appetite and inhibits the occurrence of 7,12-dimethylbenz[a]anthracene- and urethan-induced lung tumors in A/J mice. (Author abstract) (26 Refs)

48. INTERMEDIATE DOSE METHOTREXATE (IDM) IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA IN NORWAY. REPORT ON A NATIONAL TREATMENT PROGRAM.

Moe PJ, Seip M, Finne PH
Barneklinikken, Regionsykehuset i Trondheim, 7000 Trondheim, Norway
Haematologia (Budap); 14(3):257-263 1981

Results of intermediate-dose methotrexate (MTX) with leukovorin rescue as treatment in hospitalized patients following induction therapy were investigated in 95 children with acute lymphocytic leukemia. Induction therapy consisted of vincristine and steroids followed by L-asparaginase for 10 days. After complete remission had been achieved three iv infusions of MTX were given at 3-wk intervals, with one-third of the dose given as a bolus. A single dose of leukovorin, 12 mg/square meter (m2), was given 24 hr after the iv MTX. At the start of induction therapy, each patient received intrathecal MTX (12 mg/m2); all but six patients received a total of eight such doses. During the maintenance phase, patients received 6-mercaptopurine, vincristine, prednisone, and MTX. During a median follow-up period of 36 mo, only 15 relapses occurred. Twelve patients, of whom 5 were in continuous complete remission, died during the follow-up period. According to probability curves, approx two-thirds of the patients were still in remission at 57 mo. Incidences of CNS leukemia and combined systemic CNS leukemia were low (5 cases diagnosed during the study). Testicular involvement was not present in any of the 58 boys studied, suggesting that routine testicular biopsy is unnecessary when using this protocol. (6 Refs)

49. EFFECTS OF ANDROSTANES ON APLASTIC ANEMIA - A PROSPECTIVE STUDY.

Hirota Y
Blood Disease Center, Nagoya Natl. Hosp., Nagoya, Japan
Nippon Ketsueki Gakkai Zasshi; 44(7):1341-1359 1981

A prospective study of the efficacy and side effects of anabolic steroids on aplastic anemia was performed, and the following conclusions were obtained. Regardless of the kinds used, the anabolics as a therapeutic drug against aplastic anemia was effective. From the observations through follow up for a prolonged period, it was suggested that anabolic therapy should be continued for 1 to 1 1/2 yr in all cases. Age, sex, type of disease (primary or secondary) had no bearing on the efficacy of anabolic therap y. Higher doses show a tendency to produce a higher efficacy rate; however, the difference is not statistically significant. The effectiveness of anabolic therapy does not depend on the profile of the patients observed at the beginning of treatment. It is a recognized fact that this drug should be administered for a long time, but the treatment has to be terminated quite often because of the appearance of side effects. The most troublesome side effect is hepatic dysfunction. The serum enzymes GOT and GPT exceed the max normal range in more than 70% of the cases. Other side effects are jaundice virilization, diabetes and hypertension. Of the drugs used, nandrolone decanoate which was administered im showed the lowest incidence of functional disorder of the liver. The clinician should try to detect the side effects such as hepatic tumors, necrosis of the head of the femur, leukemia, progressive dysfunction of the liver, venous thrombosis and diabetes in the late stage of these disorders. From our studies so far on the corticosteroids, we have not been able to find a hemopoietic activity in these compounds. From the results of these studies the significance of the anabolic steroids as an effective therapeutic agent against aplastic anemia seems to be fully recognized. Androgen (anabolic steroid) therapy does contribute to the prolongation of life following the initiation of their administration to patients afflicted with aplastic anemia. (36 Refs)

50. HORMONE DEPENDENCY AND HISTOLOGICAL TYPES OF PROSTATIC CARCINOMA.

Schubert GF, Volter D, Ziegler H
Inst. Pathology, Municipal Hosp., Wuppertal, W. Germany
Int Urol Nephrol; 13(3):271-274 1981

Effects of hormone therapy on prostatic carcinoma (PC) and correlations between malignancy grading and hormonal dependency were studied. Histological and cytological examinations were conducted in 270 patients with PC. The tumor-grading system for malignancy was reduced to three grades to examine histological and cytological hormone therapy effects on the tumor. Orchiectomy was performed in 147 patients, and after an initial massive dose (10 g) of stilbendiphosphate the patients received 100 mg estradiol every 3-4 wk. Cytologic follow-up study showed that 38% of moderately differentiated carcinomas responded favorably, and 81% of poorly differentiated tumors showed no reaction. Reaction to hormonal estrogen therapy was good to moderate in 71 patients and negative in 76 patients. Histological examination showed distinct response in 66.6% of highly differentiated and in 42.8% of moderately differentiated carcinomas. In histological slides, responsive regressive changes were also seen in 15 poorly differentiated carcinomas. During the first 3 mo of therapy the regressive changes of poorly differentiated carcinomas were irrelevant for the prognosis. True squamous metaplasia appeared in normal and adenomatous glands only, although changes resembling squamous metaplasia were also seen in carcinoma cells. An early and reliable sign of response to hormone therapy proved to be reticularization and vacuolization of the nuclear chromatin. Follow-up studies by multiple aspiration biopsy with cytologic examination appear to be more reliable in prognostic terms than histological examination of the tumor structure. (5 Refs)

51. REDUCTION OF PROLINE TRANSPORT IN R3230AC MAMMARY CARCINOMAS BY ESTROGENS IN VITRO.

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Dept. Biochemistry, Univ. Rochester Medical Center, 601 Elmwood Ave., Rochester, NY, 14642

Biochem Pharmacol; 31(1):37-41 1982

The effects of estrogens on proline and leucine transport into enzymatically dissociated cells from the R3230AC mammary adenocarcinoma were studied. Estradiol-17beta demonstrated a time- and dose-dependent reduction of proline transport; at 10(-6) M, transport of proline was decreased by 50%. Kinetic analysis of these effects indicate that estradiol displayed characteristics of a noncompetitive inhibitor, with a Ki of 1.79 uM. Other estrogens, and the anti-estrogen tamoxifen, gave somewhat higher estimated Ki values and could be ranked as inhibitors as follows: estradiol-17beta greater than diethylstilbestrol greater than tamoxifen greater than estriol approx = estrone greater than estradiol-17 alpha. No effects of these estrogens on leucine transport were observed, indicating their selectiveness for the A system. The synthetic glucocorticoid, dexamethasone, was comparable to diethylstilbestrol as an inhibitor of proline transport, but dexamethasone also decreased transport of leucine. Testosterone and progesterone were approximately comparable to estrone in their actions. It is proposed that these actions of estrogens represent one potential mechanism whereby pharmacological levels exert therapeutic benefit in the treatment of advanced breast cancer. (Author abstract) (23 Refs)

52. NEONATAL STIMULATION OF THE UTERUS BY CLOMIPHENE, TAMOXIFEN AND NAFOXIDINE: RELATIONSHIP TO THE DEVELOPMENT OF REPRODUCTIVE TRACT ABNORMALITIES.

Clark JH, Guthrie SC, McCormack SA

Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030

Adv Exp Med Biol; 138:87-98 1982

Single injections of clomid or Nafoxidine in rats during fetal and neonatal life caused a wide variety of abnormalities of the reproductive tract. Sustained estrogenic stimulation of the neonatal rat uterus was specific for the epithelial cell stimulation due to triphenylethylene derivatives (tamoxifen). Single injections of steroid hormones had little or no stimulatory effect. The triphenylethylene derivatives probably act directly on the target tissues. Caution in the use of these compounds in humans is recommended. (37 Refs)

53. COMPARATIVE ANTIOESTROGEN ACTION IN EXPERIMENTAL BREAST CANCER.

Jordan VC

Dept. Human Oncology and Pharmacology, Wisconsin Clinical Cancer Center, univ. Wisconsin, 600 Highland Ave., Madison, WI, 53792

Adv Exp Med Biol; 138:165-178 1982

A comparative assay system based upon the treatment of animals with early microfoci of carcinogen transformed breast cells by a 1 mo course of antiestrogen therapy was devised. Effectiveness of therapy in controlling the future development of tumors was studied using the assay. In the 7,12-dimethylbenz(a)anthracene-induced rat carcinoma mammary model, tamoxifen appears to be a more potent antitumor agent than the short acting monohydroxytamoxifen. (19 Refs)

54. INHIBITION OF ESTROGEN BIOSYNTHESIS AND REGRESSION OF MAMMARY TUMORS BY AROMATASE INHIBITORS.

Brodie AM, Brodie HJ, Romanoff L, Williams JG, Williams KI, Wu JT

Worcester Foundation for Exerimental Biology, Shrewsbury, MA, 01545

Adv Exp Med Biol; 138:179-190 1982

Inhibition of estrogen biosynthesis and regression of mammary tumors by aromatase inhibitors (AI) were studied in vitro utilizing the human placental and pregnant mares' serum gonadotropin (PMSG)-primed rat ovarian microsomal system. Compounds studied were 4-hydroxyandrostene-3,17-dione, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstratriene-3,17-dione. Effects of AI on mammary tumors were also studied and metabolic studies with AI conducted. (27 Refs)

55. BIOLOGIC ACTIVITY OF THE IODOESTROGENS AND THEIR USE IN BREAST CANCER.

Longcope C, Arunachalam T, Rafkind I, Caspi E

Worcester Foundation for Experimental Biology, Shrewsbury, MA, 01545

Adv Exp Med Biol; 138:191-210 1982

The biological activity of iodinated estrogen analogues is reported and their use in breast cancer is discussed. 6-Iodoestra-1,3,5(10),6-tetraene-3,17beta-diol, 16alpha-iodoestradiol, and 16beta-iodoestradiol displaced 3H-estradiol from the uterine cytosol receptor by competitive inhibition. These estrogens translocated the cytosol receptors to the nucleus in vitro and increased mouse uterine wt in vivo. As imaging agents in the rat, sc, iv, or ip injection resulted in uptake in various organs and in some tumors, depending on the agents used. (23 Refs)

56. DEACYLCORTIVAZOL, A POTENT GLUCOCORTICOID WITH UNUSUAL STRUCTURE AND UNUSUAL ANTI-LEUKEMIC CELL ACTIVITY.

Thompson EB, Simons SS, Harmon JM

Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, Bethesda, MD, 20205

Adv Exp Med Biol; 138:315-324 1982

Induction of tyrosine aminotransferase (TAT) and lympholysis of T-derived leukemic lymphoblasts by deacylcortivazol (DAC) were investigated in HTC rat hepatoma cells and CEM-C7 human acute leukemic lymphoblasts. Two toxic effects on lymphoblasts were observed: the classic gluco corticoid effect with high potency and the ability of the compound to kill completely glucocorticoid-resistant clones irrespective of their residual receptor content. DAC was approx 400x more potent than cortisol in inducing TAT. DAC and similar compounds may have chemotherapeutic potential for certain blood dyscrasias. (22 Refs)

57. EVALUATION OF IN VIVO AND IN VITRO RESPONSES OF ENDOMETRIAL ADENOCARCINOMA TO PROGESTINS.

Holinka CF, Deligdisch L, Deppe G, Fleming H, Namit C, De la Pena MM, Gurpide E
Dept. Obstetrics and Gynecology, Mount Sinai Sch. Medicine, New York, NY, 10029
Adv Exp Med Biol; 138:365-376 1982

In vivo and in vitro effects of progestins on endometrial cancer (EC), correlation between progesterone receptor levels and histologic changes after medroxyprogesterone acetate (MPA) administration, and properties of monolayer cultures of epithelial cells from endometrial adenocarcinoma (EA) were studied. Results of MPA treatment on EA and of estradiol 17beta dehydrogenase activity in EC in organ culture are presented. (34 Refs)

58. COMBINED ADJUVANT CHEMO-ENDOCRINE THERAPY OF MAMMARY CARCINOMA.

Kubista E, Salzer H, Spona J, Aiginger P
I. Universitats-Frauenklinik, Spitalgasse 23, A-1090 Wien, Austria
Gynaekol Rundsch; 21(Suppl2):28-31 1981

An ongoing study of combined adjuvant therapy of breast cancer, combining cytostatic (CT), hormonal (HT), and radiation (RT) therapy, is described. Patients undergo a modified radical mastectomy with preservation of breast musculature and dissection of the axilla following radioisotopic marking of lymph nodes. Patients are classified as premenopausal (PRM) or perimenopausal with low serum levels of follicle stimulating hormone, and estrogen- and progesterone-receptor status is determined. RT is administered for locoregional tumor control. CT is begun 10-14 days after surgery and consists of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or Nolvadex. Patients with receptor-negative (R-) tumors and lymph node metastases (LNM) received 6-12 cycles of CMF. Receptor positive (R+) patients with LNM undergo ovariectomy as part of ablative HT. Ablative HT is combined with additive HT. R- patients and PRM R+ patients without LNM do not undergo ovariectomy. R+ patients with LNM receive CMF, ovariectomy, ovariectomy plus CMF, or ovariectomy plus Nolvadex. Results of the study will be combined with those of another large-scale cooperative study. (5 Refs) (In GER)

59. TREATMENT OF HORMONE-RESISTANT CARCINOMA OF THE PROSTATE.

Shiomi T, Yoshida K, Sanma S, Komada S, Sasaki K, Maruyama Y, Hirao Y, Hiramatsu T, Okajima E
Dept. Urology, Nara Medical Univ., Kashihara, Japan
Hinyokika Kiyo; 27(10):1291-1296 1981

Ninety-three patients with prostatic carcinoma were treated at Nara Medical University between April 1969 and March 1980. The average age of patients was 70.6 years old and the age range was between 50 and 87. Ninety-one patients of whom had histologically proved adenocarcinoma, and 2 patients had proved transitional cell carcinoma of the prostate. Initial clinical stage was as follows: Stage A 7 cases (7.5%), Stage B 6 cases (6.5%), Stage C 39 cases (41.9%) and Stage D 41 cases (44.1%). Histological grade was determined as follows: well differentiated type 20 cases (21.5%), moderately differentiated type 53 cases (57.0%), poorly differentiated type 9 cases (9.7%) and unidentified 9 cases (9.7%). Of 93 patients, 66 were treated with anti-androgen therapy, and 21 were treated with radiotherapy and/or chemotherapy because they had no response to initial hormonal manipulation, and the remaining 6 cases underwent radical prostatectomy with adjuvant anti-androgen therapy. Relapse was seen in 20 patients: 15 were in the group of anti-androgen therapy, 4 were in the group of radiotherapy and/or chemotherapy following anti-androgen therapy and 1 was in the group of radical prostatectomy. The interval to relapse was 2.2 years on the average (range: 8 months to 6 years). Five year actuarial survival rates were 37.7% in the group of anti-androgen therapy, and 61.9% in the group of radiotherapy and/or chemotherapy, and the significant difference between these two groups was not seen. The five patients diagnosed as Stage D adenocarcinoma of the prostate, four of whom had multiple bone metastasis and two had liver metastasis in addition to bone metastasis, showed favorable response to the administration of Cis-DDP. (Author abstract) (34 Refs) (In JPN)

60. 5 CASES OF HORMONE-RESISTANT PROSTATIC CANCER.

Miyakoda K, Mishina T, Kobayashi T, Maekawa M, Oohe H, Watanabe H
Dept. Urology, Kyoto Prefectural Sch. Medicine, Kyoto, Japan
Hinyokika Kiyo; 27(10):1303-1307 1981

Among five cases of hormone-resistant prostatic cancer, two were treated by radiation and intraprostatic injection of bleomycin. Two other cases were treated by cryosurgery and chemotherapy combined with estrogen administration, and the remaining one case by medical adrenalectomy. According to Karnofsky's criteria, one case was judged as 1-C, two cases as 1-B, one case as 1-A, and one case as 0-O. The effective rate was 80%. (Author abstract) (16 Refs) (In JPN)

61. CUSHING'S DISEASE: TRANSIENT SECONDARY ADRENAL INSUFFICIENCY AFTER SELECTIVE REMOVAL OF PITUITARY MICROADENOMAS; EVIDENCE FOR A PITUITARY ORIGIN.

Fitzgerald PA, Aron DC, Findling JW, Brooks RM, Wilson CB, Forsham PH, Tyrrell JB
Metabolic Res. Unit, Univ. California,, 1143 HSW, San Francisco, CA, 94143
J Clin Endocrinol Metab; 54(2):413-422 1982

Of 12 patients with Cushing's disease who had successful selective microadenoma resection documented by clinical remission and reversal of hypercortisolism, 11 developed postoperative hypoadrenalism with deficient adrenal responsiveness to exogenous ACTH. The ACTH and glucocorticoid deficiency was not caused by the surgical procedure or hydrocortisone replacement, since it resolved despite replacement therapy; further, adrenal insufficiency did not occur in 10 acromegalic patients who received the same operation and identical glucocorticoid therapy. Other pituitary functions were not impaired postoperatively. We conclude that (1) the hypercortisolism caused by an ACTH-secreting pituitary microadenoma suppresses the normal pituitary secretion of ACTH and often that of GH and LH; (2) this suppression persists postoperatively, but gradually resolves in most patients; (3) a normal cortisol response to ACTH is a good indication that the pituitary-adrenal axis has recovered; (4) there is no evidence of a persisting hypothalamic defect after removal of ACTH-secreting microadenomas; and (5) pituitary microadenomas appear to be the primary cause of Cushing's disease in these patients. (65 Refs)

62. HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN ADVANCED CHEMOTHERAPY-RESISTANT OVARIAN CARCINOMA: A PHASE II STUDY.

Aabo K, Pedersen AG, Hald I, Dombernowsky P
Dept. Chemotherapy R II, Finsen Inst., 49-Strandboulevarden, DK-2100 Copenhagen, Denmark
Cancer Treat Rep; 66(2):407-408 1982

The Phase II trial of high-dose medroxyprogesterone acetate (MPA: 500 mg/square meter/day in 3 fractions, po) was carried out in 30 patients (39-72 yr old) with histologically verified Stage III-IV ovarian adenocarcinoma. The duration of MPA treatment was 1-6 mo. Of 27 evaluable patients, only 1 had greater than 50% reduction of metastatic neck lymph nodes and of epigastric mass. There was no MPA-induced toxicity. (5 Refs)

63. MAMMARY TUMOR INHIBITING EFFECT OF 3,3'-DIACETOXY-ALPHA,BETA-DIALKYLSTILBENES AND OF RELATED STILBENE OXIDES.

Schneider MR, Schonenberger H, Michel RT, Fortmeyer HP
Institut fur Pharmazie der Universitat Regensburg, Universitatsstrasse 31, D-8400 Regensburg, W. Germany
J Med Chem; 25(2):141-145 1982

The compounds 3,3'-Diacetoxy-alpha,beta-dialkylstilbenes (alkyl = CH3 to C4H9, 1-4), 3,3'-dihydroxy-alpha,beta-diethylstilbene (5), and their corresponding oxides were synthesized. Compounds 1-10 competitively antagonized in vitro the interaction of [3H]estradiol with its receptor. 3,3'-Diacetoxy-alpha,beta-diethylstilbene (2), 3,3'-diacetoxy-alpha,beta-diethylstilbene oxide (7), and their phenolic analogues (5 and 10) were most effective. Shortening or lengthening the alkyl side chains led to a decrease in receptor affinity. Among the stilbenes and epoxides, those with C2H5 and C3H7 groups (2,3,5 and 7,8,10) caused the strongest inhibition of the growth of a hormone-dependent postmenopausal human mammary carcinoma serially implanted in nude mice. The strong antitumor activity of 5 and 10 was confirmed by experiments on the 9,10-dimethyl-1,2-benzanthracene-induced, hormone-dependent mammary carcinoma of the Sprague-Dawley rat. (Author abstract) (10 Refs)

64. EFFECT OF ESTRADIOL AND DEGREE OF CELL DIFFERENTIATION ON HUMAN MELANOMA SUSCEPTIBILITY TO KILLING BY MONOCLONAL ANTIBODIES.

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Immunol Lett; 4(1):59-64 1982

The relationship of antigenic determinants of melanotic and amelanotic human malignant melanoma cells to responsiveness to estradiol (ES) was studied. Cultures grown in the absence and presence of ES were used to develop various cell lines: a non-responsive melanotic (E-M+ShA) was derived from ES-responsive melanotic (E+M+ShA) and an ES-responsive amelanotic (E+M-SR) was derived from ES-non-responsive amelanotic (E-M-SR). Cellular responsiveness to hormone was determined by incubation with insulin, with addition of (3H)thymidine after 72 hr. Spleen lymphocytes from mice preimmunized with E+M+ShA, E-M+ShA, E-M-SR, and E+M-SR were fused with murine non-producer myeloma cells to obtain mouse-mouse hybridoma cultures synthesizing monoclonal antibodies against human malignant melanoma. Complement-dependent cytotoxic activity of the monoclonal antibodies varied from one hybridoma to another. Results indicate that the antigenic determinants of melanoma cells vary from one cell line to another; efficiency of complement-mediated killing is a function of responsiveness to estradiol and degree of melanogenesis. (37 Refs)

GENERAL REVIEWS ON STEROID HORMONES

65. REPRODUCTIVE FUNCTION IN RELATION TO BREAST CANCER RISK.

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Excerpta Med Int Congr Ser; 551:224-233 1981

Factors which mediate breast cancer (BC) risk are discussed. While it has been reported that estrogens may decrease BC risk, in patients with estrogen-dependent BC they may accelerate malignant growth. While the proliferative action of estrone and estradiol have been linked to BC, the rise in BC incidence with advancing age parallels the gradual fall in estrogens. Estriol and 2-hydroxy-estrone protect the breast from estradiol-estrone hyperstimulation and carcinogenesis. Increased androgen conversion to estrone may stimulate epithelial proliferation of breast tissues toward overt carcinoma. Early menarche increases BC risk nearly twofold, while married women experience a twofold lower risk than unmarried women. Parous women have a two- to fourfold decrease in BC risk as compared to nonparous women. BC risk is increased in women undergoing late menopause. Bilateral ovariectomy before the age 40, early pregnancy, and extended lactation may protect against BC, while high parity coupled with early pregnancy, or late first pregnancy increase risk. (37 Refs)

66. BILATERAL ACOUSTIC NEUROMAS: CLINICAL ASPECTS, PATHOGENESIS, AND TREATMENT.

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Neurosurgical Service, Massachusetts General Hosp., Boston, MA, 02114

Neurosurgery; 10(1):1-12 1982

The cases of 15 patients (9 female, 14-74 yr old; 6 male, 12-32 yr old) with bilateral acoustic neuromas are described. The technical surgical problems, results of treatment, and complications of this illness are discussed. Eleven of the patients had no family history of neurofibromatosis or CNS tumor, and a spontaneous mutation is considered to be responsible for the initiation of disorders in these patients. Most of the patients were 21 yr old or younger when their symptoms began; they had a more fulminant course and a higher incidence of multiple CNS tumors than those who developed symptoms later. Evidence that 17-beta-estradiol may be an important part of the tumor growth control mechanism is presented, and it may explain why Schwann cell tumors preferentially occur in the vestibular nerve, trigeminal nerve, and spinal sensory nerves. Genetic aspects and potential treatment alternatives of bilateral acoustic neuromas are discussed. (51 Refs)

67. DRUG INTERACTION WITH ESTROGEN RECEPTORS FOR THE CONTROL OF BREAST NEOPLASIA (REVIEW).

Leclercq G, Heuson JC
Laboratiore et Clinique de Cancerologie mammaire, Service de Medicine, Institut J. Bordet, 1000 Brussels, Belgium
Anticancer Res; 1(4):217-228 1981

Major characteristics of most drugs that interact with estrogen receptors (ER) and are of potential value in treatment of breast cancers and other estrogen-sensitive neoplasias are reviewed. Drugs should present a maximal binding affinity for ER as well as minimal affinity for the non-receptor sites in order to be selectively taken up by the target tissues. Binding of estrogens and antiestrogens to ER depends on interaction with the hydrophobic pocket or the region binding the aminoalkyl side chain. Activity of the drugs depends on binding characteristics, effects on growth of human breast cancer cell lines, and in vivo properties. Triphenylethylene antiestrogens translocate cytoplasmic ER to the cell nucleus. Use of tamoxifen has been prompted by the lack of major side effects. Compounds with potential therapeutic value and active compounds of antiestrogens are presented. Estrogen-linked cytotoxic agents estradiol mustard and estracyt have been tested for treatment of advanced breast cancer; neither displayed significant binding affinity to ER. Antitumor activity of estrogens bearing a cytotoxic group or gamma-emitting radionuclide has not been confirmed, since ER can only be assessed by biochemical assays in tissue samples . A scintigraphic technique giving in vivo estrogen receptivity of a mammary cancer could provide valuable diagnostic and therapeutic information. (94 Refs)

OTHER RELATED STUDIES

68. MENOPAUSE.

Kaye HL
Univ. Texas Health Science Center, Dallas, TX
Curr Ther; 28:913-914 1981

Therapy during menopause is discussed. Recent publications (many in the lay press) have raised concern over the carcinogenic potential of estrogen treatment. Estrogens, when used cyclically in the lowest effective dose, are highly effective in improving the quality of life. Abnormal bleeding must be diagnosed before the start of therapy. All postmenopausal bleeding must be evaluated by biopsy or curettage. No evidence exists that estrogens cause breast cancer. (no Refs)

69. ENDOCRINE INTERRELATIONSHIPS IN PATIENTS WITH MALIGNANT TESTICULAR TUMORS.

Lunglmayr G, Kuber W, Spona J
Urologische Universitatsklinik, Alser Strasse 4, A-1090 Wien, Austria
Wien Klin Wochenschr; 93(13):411-414 1981

In 40 patients (16-47 yr old) with malignant germinal testicular carcinoma spermatologic and endocrinologic analyses were conducted. The specific endocrine activity of tumor tissue was determined through the beta-HCG level in serum before therapy. Beta-HCG positive results were obtained in 21 patients, beta-HCG negative results in 19 patients. Follicle stimulation hormone production of pituitary gland was suppressed by increased estradiol production due to increased beta-HCG production. The elevated estrogen level in serum was also the cause of gynecomasty. Spermiograms were strongly affected in all cases. (17 Refs) (In GER)

70. BIOCHEMICAL AND ESTROGENIC ACTIVITIES OF SOME DIETHYLSTILBESTROL METABOLITES AND ANALOGS IN THE MOUSE UTERUS.

Korach KS
Lab. Reproductive and Developmental Toxicology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Adv Exp Med Biol; 138:39-62 1982

Estrogenic activity and intracellular mechanism of (2,4,6,7-3H)estradiol-17beta, indenestrol A, indenestrol B, indanestrol, pseudo-diethylstilbestrol, and some other steroid compounds were examined and their action in the mouse uterus was studied. A major point in the study involved determination of the discrepancy between the in vitro and in vivo hormone activities. (58 Refs)

71. THE SEARCH FOR PROGESTERONE-DEPENDENT PROTEINS SECRETED BY HUMAN ENDOMETRIUM.

MacLaughlin DT, Sylvan PE, Richardson GS
Vincent Memorial Hosp., Boston, MA
Adv Exp Med Biol; 138:113-131 1982

Studying the mechanism of action of progesterone on human endometrium, analysis of uterine luminal fluid was carried out to identify gene products for this steroid. Results showed that human uterine fluid contains a group of proteins not present in serum that are detectable mainly in the secretory phase of the menstrual cycle and that the proteins may be progesterone-induced products of human endometrial secretion. (75 Refs)

72. A COMPARATIVE STUDY OF THE ESTROGENIC EFFECTS OF TAMOXIFEN AND 17 BETA-ESTRADIOL IN POSTMENOPAUSAL WOMEN.

Helgason S, Wilking N, Carlstrom K, Damber MG, Von Schoultz B
(c/o von Schoultz) Dept. Obstetrics and Gynecology, Univ. Umea, S-901 87 Umea, Sweden
J Clin Endocrinol Metab; 54(2):404-408 1982

The effects of tamoxifen and 17 beta-estradiol on the levels of FSH, PRL and pregnancy zone protein were compared in two groups of postmenopausal women. Seventeen women with breast cancer were treated with tamoxifen (20 mg, twice a day). Fourteen women with climacteric complaints were given 17 beta-estradiol (2 mg, daily). A close parallelism between the effects of 17 beta-estradiol and the antiestrogen was obtained in all three markers studied. The percent decreases in FSH after 1 mo were 29 and 44 and, after 3 mo, 26 and 34 in the tamoxifen and estradiol groups, respectively. The decreases in PRL after 1 and 3 mo of treatment with tamoxifen were 36% and 71%, and 19% and 31% after treatment with estradiol. Both treatments increased PZP serum levels, tamoxifen by 32% and 44% and estradiol by 55% and 70% after 1 and 3 mo. Thus, tamoxifen was found to exert weak estrogenic effects in postmenopausal women. (Author abstract) (35 Refs)

73. EFFECTIVE CONTROL OF CISPLATIN-INDUCED NAUSEA USING HIGH-DOSE STEROIDS AND DROPERIDOL.

Mason BA, Dambra J, Grossman B, Catalano RB
Graduate Hosp., One Graduate Plaza, 19th and Lombard St., Philadelphia, PA, 19146
Cancer Treat Rep; 66(2):243-245 1982

Seventy-three consecutive patients receiving cisplatin-containing chemotherapy regimens were treated with an initial dose of chlorpromazine (25 mg im), droperidol (1 mg iv, then 1 mg sc every 4 hr), and methylprednisolone (250 mg every 4 hr for 4 doses). Twenty patients received a combination chemotherapy protocol that included cisplatin at a dose of 40 mg/m2 iv (Group 1) and 53 patients received a protocol that included cisplatin at a dose of 120 mg/m2 iv (Group 2). The median age of all the patients was 58 yr. Seventy-five percent of the patients in Group 1 and 45% of those in Group 2 had no vomiting at all; the remainder had limited and tolerable vomiting. These results in a group of elderly patients compare favorably with trials of other antiemetic programs. (Author abstract) (17 Refs)

74. ACTH SECRETING PITUITARY ADENOMA IN AN INFANT OF 18 MONTHS. IMMUNOHISTOCHEMICAL, ELECTRON- MICROSCOPIC, AND IN-VITRO STUDIES.

Saeger W, Ruttmann E, Ludecke D
(c/o Saeger) Abteilung fur Pathologie, Marienkrankenhaus, Alfredstr. 9, 2000 Hamburg 76, W. Germany
Pathol Res Pract; 173(1/2):121-129 1981

An 18-mo old infant with Cushing's disease due to an ACTH producing pituitary tu mor is presented. The case showed typical clinical and morphological signs of hypercortisolism. The infant died of pulmonary thrombembolism after transsphenoidal partial adenomectomy. The adrenals were diffusely hyperplastic. The pituitary adenoma was classified as an undifferentiated mucoid cell adenoma with sparse granulation by light microscopy. Immunoenzymatic studies demonstrated ACTH not only in granulated adenoma cells. Ultrastructurally the cells were only differentiated as typical ACTH cells or so-called follicular cells in small areas. Most of them were undifferentiated, showing pleomorphism of the relatively sparse organelles. In-vitro experiments using suspensions of adenoma cells showed a distinct enhancement of ACTH secretion after arginine-vasopressin and a further decrease ultrastructurally in the number of secretory granules. No effect on ACTH levels and no alterations of the ultrastructure were observed after cortisol. The case is representative of typical hypothalamic-hypophyseal Cushing's disease with an undifferentiated pituitary adenoma secreting ACTH in part autonomously. This constellation of Cushing's syndrome is extremely rare at the age of 1 yr. Our case is the second one reported in the literature. (Author abstract) (17 Refs)

75. HIGH-DOSE DEXAMETHASONE FOR PREVENTION OF CIS-PLATIN-INDUCED VOMITING.

Aapro MS, Alberts DS

Sect. Hematology/Oncology, Arizona Health Sciences Center, Tucson, AZ, 85724

Cancer Chemother Pharmacol; 7(1):11-14 1981

A pilot study of high-dose dexamethasone (DEX) with or without a neuroleptic for the control of chemotherapy-related emesis is reported. The antiemetic regimen consisted of 8 mg DEX po the night before treatment, and 4 mg DEX every 4-6 hr on the day of treatment, supplemented by 10 mg iv just before chemotherapy. Steroid dose was tapered over the next few days. Droperidol or haloperidol, 2.2.5 mg iv were also administered to 19 of the 34 patients in this trial. Twenty-eight patients received cis-platinum in doses of 50-75 mg/square meter (m2) every 3-4 wk or 20 mg/m2 for 5 days every 3 wk in various drug combinations, including (1) cis-platinum- mitomycin C-vincristine-bleomycin; (2) cis-platinum- adriamycin-cyclophosphamide; (3) cis-platinum- adriamycin-vinblastine; (4) cis-platinum- adriamycin-cyclophosphamide-bleomycin-vincristine mitomycin C; (5) cis-platinum-vinblastine-bleomycin-hexamethylmelamine; and (6) cis-platinum-5-fluorouracil-vinblastine-bleomycin. Six patients were treated with non-platinum-containing drug combinations, including actinomycin D, dacarbazine, hydroxyurea, adriamycin, cyclophosphamide, and carmustine. Seven patients had only one treatment and all others had two or more. Five/10 patients who had previously failed to respond to other antiemetics had an excellent or good response to DEX regimens. Among 24 patients who received DEX from the beginning of anticancer therapy 62% (neuroleptics added)-82% (no neuroleptics) had excellent or good antiemetic responses. (30 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. STEROID ENZYME ACTIVITIES IN EXTRAADRENAL PHEOCHROMOCYTOMAS.

Carballeira A, Fishman LM
Veterans Admin. Medical Center (151), 1201 N.W. 16th St., Miami, FL, 33125
J Clin Endocrinol Metab; 54(3):619 1982

The adrenal medulla and tumors derived from it have been shown to be capable of converting radioactive steroid intermediates into glucocorticoid end products in vitro. This capacity for partial steroid synthesis was explored in two large extraadrenal pheochromocytomas and compared to the results of parallel studies with intraadrenal pheochromocytomas and adrenal cortex; in one experiment, all three types of tissue were obtained from a single patient and studied simultaneously. Slice preparations of extraadrenal pheochromocytoma transformed 14C-labeled pregnenolone (3beta-hydroxypregn-5-en-20-one) into corticosterone and cortisol. Incubations of subcellular fractions demonstrated that, as in the adrenal cortex and intraadrenal chromaffin tissue, Delta(5)-3beta-hydroxysteroid dehydrogenase-isomerase, 17alpha-hydroxylase, and 21-hydroxylase activities in extraadrenal pheochromocytomas were associated with the microsomes and 11beta-hydroxylase was associated with the mitochondria, where metyrapone was an effective inhibitor; these findings tend to dissociate steroid-metabolizing activity in chromaffin tissue from the enzymes involved in catecholamine biosynthesis, which are probably localized to different subcellular organelles. Cholesterol side-chain cleavage activity could not be detected in the mitochondria, chromaffin storage granules, or large granule fractions of either extraadrenal or intraadrenal pheochromocytomas. The capacity of intraadrenal pheochromocytomas to carry out steroid transformations was consistently greater than that of extraadrenal tumors, suggesting that the adrenal cortex may play a role in inducing enhanced steroid-metabolizing activity in the adjacent chromaffin tissue perfused by glucocorticoid intermediates in high concentrations. (Author abstract) (no Refs)

2. HORMONE-RELATED ENZYMATIC ACTIVITIES IN NORMAL AND CANCER CELLS OF HUMAN ENDOMETRIUM.

Holinka CF, Gurpide E
Dept. Obstetrics and Gynecology, Div. Reproductive Biology, Mount Sinai Sch. Medicine, New York, NY, 10029
J Steroid Biochem; 15:183-192 1981

Enzyme studies in human endometrium were conducted by measuring activities throughout the menstrual cycle in whole endometrium and in the glandular and stromal fractions, as well as under organ culture conditions and in cultures of endometrial epithelial and stromal cells. Alkaline phosphatase (AP), peroxidase (PO), and ornithine decarboxylase (ODC) were investigated. Parallel studies were carried out on specimens of endometrial cancer and on cultures of an endometrial adenocarcinoma (EAC) cell line (HEC-1B). Estradiol-17beta dehydrogenase activity was found localized preferentially in secretory glands. Administration of medroxyprogesterone acetate to patients with EAC resulted in the appearance of subnuclear vacuoles in endometrial glands. AP activity in glands isolated from fresh tissues was generally higher in proliferative than in secretory endometrium. Within 8 days after plating, decline of AP activity in primary cultures derived from glands and stroma was noticed when compared to values of fresh tissue. Relative resistance of AP to phenylalanine and its sensitivity to homoarginine and 57 C heat inactivation indicate that AP belongs to the non-placental group of organ-specific isoenzymes. Elevated PO levels were found in most cancer tissues. PO activities were higher in secretory endometrium than in proliferative tissues, and endometrial stroma is the major site of activity. ODC activity is very low or negligible in HEC-1B cells at confluence but high in proliferating cells. No ODC was present in stromal cell cultures during active growth; the enzyme could not be induced by the procedures effective with HEC-1B, indicating that enhanced ODC activity may be causally related to growth in some but not all cell types and that measurements of the enzyme may not be a reliable index of abnormal growth. (83 Refs)

3. STUDIES OF OESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN WITH CANCER.

James VH, Reed MJ, Folkerd EJ
Dept. Chemical Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
J Steroid Biochem; 15:235-246 1981

Metabolic clearance rates (MCR) and production rates (PR) for estrone (E1) and estradiol (E2) were measured in six menopausal women with endometrial cancer (EC), five with endometrial hyperplasia, and two normal women; plasma concentrations (PC) of E1 and E2 were measured in postmenopausal women with breast cancer (BC). Significant correlation was found between MCR-E1 and percent ideal body weight. In spite of the elevated MCR of E2 seen for women with EC, the normal or low PC of E2 found for these women resulted in values for the PR of E2 that were mainly similar to the range reported for normal menopausal women. In most subjects E1 accounted for less than 40% of the E2 produced. Results suggest that E1 is not the only precursor and source of E2 in postmenopausal women. Binding capacity of sex hormone binding globulin (SHBG) expressed as ug dihydrotestosterone/100 ml plasma, was similar in women with BC (2.2 -1.3), benign breast disease (1.9 -1.0), and normal women (2.5 -1.8). This supports the observation that in some BC patients the unbound E2 fraction is elevated by a mechanism other than reduced SHBG concentration. Range of conversion of androstenedione to E1 in normal adipose tissue samples was substantial, varying from 0.5-44.0 picog E1/mg protein/3 hr, indicating that the more efficient conversion reported from in vivo studies in heavier women is not due to more efficient aromatization in adipose tissue in these women, and may therefore reflect only the large amount of tissue available. Adipose tissues examined converted E1 to E2 under the experimental conditions employed demonstrating the tissue as a potentially important site of 17beta-hydroxysteroid dehydrogenase activity, and thus of E2 production. (54 Refs)

4. FECAL STEROID METABOLITES AND BREAST CANCER RISK.

Papatestas AE, Panveliwalla D, Tartter PI, Miller S, Pertsemlidis D, Aufses AH
Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029
Cancer; 49(6):1201-1205 1982

Women with breast cancer (n = 78) had a higher excretion of total fecal steroids in mg/gm of dry weight (56 37) compared to controls (45 -29; n = 71) (p = 0.03). Increases in both total neutral steroids and total bile acids in cases contributed to this significant difference. Lean women (Quetelet's index less than 3.5) with breast cancer seemed to have inappropriately high excretion of total fecal steroids (56 -35), which was significantly higher than that of controls (41 -27) (p = 0.03). Obesity resulted in higher excretion of fecal steroids only in controls. The differences persisted, even after pairing control cases for race-ethnicity and menopausal status. In 59 such pairs, cases had higher values (56 -33), compared to controls (41 -26) (p = 0.008). Significant differences (p = 0.005) were also present in 24 post-menopausal pairs, while in 35 pre-menopausal pairs a similar trend, but no significant differences were noted. Women with benign breast disease had higher total fecal steroids (51 -34) compared to the other controls (38 -21) (p = 0.05). This observation suggests a common etiology between benign breast disease and breast cancer. There were no significant differences in dietary intake of total calories, total fat or dietary cholesterol between controls and cases suggesting that the observed differences in fecal steroids could be attributed to higher endogenous synthesis of cholesterol in cases. (Author abstract) (23 Refs)

5. ESTROGEN SULFURYLATION AS AN ALTERNATIVE INDICATOR OF HORMONE DEPENDENCE IN HUMAN BREAST CANCER.

Pewnim T, Adams JB, Ho KP
Sch. Biochemistry, Univ. New South Wales, Sydney, N.S.W. 2033, Australia
Steroids; 39(1):47-52 1982

Estrogen receptor (ER) levels, formation of 3'-phosphoadenosine-5'phosphosulfate (PAPS), and sulfate transfer to estradiol-17beta, have been determined in 62 human primary carcinoma cytosol preparations. While no differences between ER positive and ER negative tumors were found in the synthesis of [35S]PAPS, formation of estradiol-3-[35S]sulfate catalyzed by estrogen sulfotransferase was significantly higher in ER positive tumors [84 -10 (mean - S.E.M.) vs 32 -9 pmole estradiol-3-sulfate per mg protein per 2 hr for ER positive and ER negative tumors, respectively, p less than 0.02]. By choosing a discriminating value for estrogen sulfurylation of 40 pmole per mg protein per 2 hr, then 16/19 (84%) of the ER negative tumors were below this point. Since previous data had shown that 20/23 (87%) progesterone receptor negative tumors were also below this value, an alternative simple method, having a high potential for the evaluation of hormone responsiveness in mammary cancer, is suggested. (Author abstract) (7 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

6. HYPERPROLACTINAEMIA IN MEN - RESPONSE TO BROMOCRIPTINE THERAPY.

Prescott RW, Kendall-Taylor P, Hall K, Johnston DG, Crombie A, McGregor A, Hall R
Dept. Medicine, Univ. Newcastle upon Tyne, Newcastle upon Tyne NE1 4LP, England
Lancet; 1(8266):245-249 1982

Men with hyperprolactinemia present with large tumors. Conventional therapy with surgery and/or irradiation is unsatisfactory, with up to 100% of patients remaining hyperprolactinemic (or subsequently developing pituitary insufficiency). In view of reports of bromocriptine-induced regression of prolactinomas, eight consecutive male hyperprolactinemic patients with impotence and/or symptoms related to local tumor effects were treated with bromocriptine 20 mg daily as sole therapy for 3-11 mo. Symptoms were relieved partly or completely in seven patients and serum prolactin was restored to normal or near normal in all men. Serum thyroxine and plasma cortisol response to hypoglycemia became normal in two men who had subnormal values before therapy. Mean serum growth hormone response to hypoglycemia rose significantly as did plasma testosterone concentrations. Evidence of tumor regression, sometimes massive, was seen in the six patients who underwent repeat radiology. The symptomatic relief and biochemical and radiological improvement in these patients indicate that bromocriptine therapy may now be the treatment of choice for hyperprolactinemic men with large tumors. (Author abstract) (37 Refs)

7. ENDOCRINOLOGICAL STUDIES OF PATIENTS AFTER SURGERY IN THE PITUITARY AREA(I).

Dolecek R, Zavada M
Department of Medicine, Regional Hospital, Ostrava, Czechoslovakia
Srp Arh Celok Lek; 109(2):197-215 1981

Ninety-four patients (61 men and 33 women; 15-73 yr old) had surgery in the pituitary area due to chromophobe adenoma (60), acromegaly (16), craniopharyngeoma (CP: 8), and others (10). Sixty three patients were studied after surgery, and 31 before and after. The study lasted 15 yr and the patients came 2-3 times a yr for follow-up. Endocrinologic tests included 17-ketosteroids (17-KS) and 17-ketogenic steroids (17-KGS) with metyrapone in urine; follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), thyroid releasing hormone (TRH), prolactin (PRL), and testosterone (TE), in plasma or serum. Except for some patients sustaining damage of vital areas, the patients were well, when receiving regular substitution therapy, and many of them returned to work. Values of 17-KS and 17-KGS were decreased. TE values in men were low, even very low, often without correlation with LH values. FSH values were a better indicator of the patients condition than LH values, although both were lower after surgery. On the contrary TRH values were not reduced in most of the patients, however, they were absent in some of them. Most pronounced changes were observed in CP patients. Activities of peripheral glands were often low even in some patients with normal levels of protein hormones. Changes in the endocrine status were observed with the passage of time; in some patients partial improvement of some hormone values was noted. (2 Refs) (In SCC)

8. STEROID HORMONE CONTENT OF BREAST TISSUE IN PATIENTS WITH MAMMARY TUMORS.

Vallent K, Feher T, Bodrogi L, Ribai Z
I. Chirurgische Klinik, Medizinische Semmelweis-Universitat, Ulloi ut 78, H-1082 Budapest, Hungary
Chirurg; 53(1):34-36 1982

Steroid hormone concentrations in plasma, in tissue from breast tumors, and in healthy breast tissue (muscle and fat) surrounding such tumors were determined by radioimmunoassays. The tissues samples were obtained from 9 patients (av age 37 yr) with benign breast tumors and 11 patients (av age 51 yr) with malignant breast tumors. The hormone concentrations in plasma were nearly identical in the two patient groups and were lower than the tissue levels. The hormone concentrations in all breast tissues of patients with benign tumors were routinely higher than the levels in breast tissues of patients with malignant tumors. (14 Refs) (In GER)

9. GONADAL DYSGENESIS WITH KARYOTYPE 46 XY IN TWO SISTERS EACH WITH A NON-RUDIMENTARY GONAD WITHOUT HISTOLOGICAL EVIDENCE OF GONADOBLASTOMA. DEMONSTRATIONS OF SECRETION OF ANDROGENS BY ONE OF THESE GONADS.

Cuvelier-Trio C, Le Capon JB, Gasnault JP, Desmons F, Buvat J, Netter, Belaisch
Service de gynecologie, C.H.U. Lille, Avenue Oscar Lambert, F59000 Lille, France
Gynecologie; 32(3):297-303 1981

Gonadal dysgenesis with karyotype 46 XY was diagnosed in two sister (21 and 25 yr old) who had gonads which were nearly normal in vol, did not correspond to gonadoblastomas, but were capable of secreting androgens. Serum estradiol was low while serum androgens were normal. A clear gradient of secretion for androstenedione, testosterone, and 17-OH-progesterone was evident in hormonal assays of blood from the efferent gonadal vein. (25 Refs) (In FRE)

10. RESPONSES OF SERUM LEVELS OF TESTICULAR STEROID HORMONES TO HCG STIMULATION IN PATIENTS WITH PROSTATIC CANCER AND BENIGN PROSTATIC HYPERTROPHY.

Isurugi K, Kanazawa M, Yanaihara T, Kambegawa A
Dept. Urology, Natl. Medical Center Hosp., Shinjuku-ku, Tokyo 162, Japan
Prostate; (Suppl1):19-26 1981

Responses of serum levels of testosterone, dihydrotestosterone (DHT), 5alpha-androstane-3-alpha-17 beta-diol (5AD), androsterone (A), and estradiol-17beta (E2) to human chorionic gonadotropin (hCG: 5,000 IU im, days 0-3 at 9 am) stimulation was measured by radioimmunoassay. Sera of 9 patients with stages C and D prostatic cancer (70-80 yr old) and 11 patients with benign prostatic hypertrophy (BPH; 59-83 yr old) were studied. Testosterone levels were significantly different between the two groups of patients, but showed similar patterns of stimulation, rising to a peak on days 2-3. No significant differences between the two groups were observed in levels of DHT, free or conjugated A, E2 or 5AD. Responses to hCG stimulation were most marked for testosterone, E2, and DHT, and less in A and 5AD. It is tentatively concludeds that an age-related prevalence of estrogens over androgens seems to exist. (22 Refs)

11. HORMONAL PATTERN IN PROSTATIC CANCER. I. CORRELATION WITH LOCAL EXTENT OF TUMOUR, PRESENCE OF METASTASES AND GRADE OF DIFFERENTIATION.

Rannikko S, Kairento AL, Karonen SL, Adlercreutz H
II Dept. Surgery, Dept. Clinical Chemistry, Univ. Helsinki, Helsinki, Finland
Acta Endocrinol (Copenh); 98(4):625-633 1981

In 32 subjects with histologically and/or cytologically verified prostatic cancer the hormonal pattern was studied by assaying 18 plasma and urinary hormones or groups of hormones. The tumors were classified according to the UICC classification system and the hormone values were correlated to the local extent of the tumor (T classification), the presence of metastases (M classification) and the differentiation grade (G classification). It was found that patients with metastases had significantly higher plasma estradiol and lower testosterone/estradiol and testosterone/estrone plus estradiol ratios as compared to those subjects without metastases. In subjects with moderately or poorly differentiated tumors plasma estrone estradiol was significantly higher and the testosterone/estrone estradiol ratio was significantly lower than in the subjects with well differentiated tumors. In the various TNM classification groups no obvious trends were found with regard to urinary hormones and no significant differences between the groups for plasma FSH, LH, prolactin, progesterone and cortisol were observed. It is concluded that in more advanced cases with metastatic cancer and when tumors are less well differentiated the androgen/estrogen ratio may be decreased. These alterations have no diagnostic significance because of great overlapping of individual results between the various groups of patients. (Author abstract) (48 Refs)

12. HORMONAL PATTERN IN PROSTATIC CANCER. II. CORRELATION WITH PRIMARY RESPONSE TO ENDOCRINE TREATMENT.

Adlercreutz H, Rannikko S, Kairento AL, Karonen SL
II Dept. Surgery and Dept. Clinical Chemistry, Univ. Helsinki, Helsinki, Finland
Acta Endocrinol (Copenh); 98(4):634-640 1981

In 32 subjects with histologically and/or cytologically verified prostatic cancer the hormonal pattern was studied by assaying 18 plasma and urinary hormones or groups of hormones and rel ating the values to the response to endocrine treatment. Total orchidectomy (orchiepididymectomy) was performed on 9 patients, subcapsular orchidectomy on 13 patients and estrogen therapy with Estradurin was given in 4 patients. Six patients had total orchidectomy followed by estrogen therapy. With few exceptions all values were within the normal range. The only significant exceptions were the high urinary estrogen values and the low urinary estrone estradiol-estriol ratio observed as compared to healthy males working in a factory. No urinary hormone values or ratios of hormone values could be used for the prediction of prognosis in prostatic carcinoma patients. However, the ratios of plasma testosterone/estradiol (T/Oe2) and testosterone/prolactin (T/Prl) were found to give good information with regard to the response to endocrine treatment. High values for one or both of these ratios meant a good response to treatment in all subjects without exception in this material. Subjects with both ratios low had a good response to endocrine treatment in 50% of the cases. No other plasma hormones measured were of any help prognostically. It is concluded that by measuring the T/Oe2 and T/Prl ratios it seems possible to select a group of patients with favorable primary response to endocrine treatment. (Author abstract) (27 Refs)

13. HYPOTHALAMIC-PITUITARY-TESTICULAR FUNCTION IN MEN WITH PRL-SECRETING TUMORS.

Ambrosi B, Gaggin M, Travaglini P, Moriondo P, Elli R, Faglia G
Clinica Medica 2, Unita Endocrina, Pad. Sacco, via F. Storza 35, 20122 Milano, Italy
J Endocrinol Invest; 4(3):309-315 1981

Levels of serum prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and 17 beta estradiol (E2) were determined in 33 men (16-64-yr-old; mean 42 yr) with PRL-secreting tumors. Patients with signs of Cushing's disease, Nelson's syndrome, or acromegaly were excluded. Hormone levels were determined before and after administration of human chorionic gonadotropin (hCG: 5,000 im for 3 days), gonadotropin-releasing hormone (GnRH: 100 ug iv), clomiphene citrate (CC: 100 mg/day for 5 days), and metoclopramide (MC: 20 mg iv) to selected groups of patients.

Mean increase in T level was significantly less in the 14 patients tested than in normal adult men; serum T increase was correlated with FSH levels, but not with those of LH and PRL, and serum E2 increase after treatment was significantly lower in patients than controls. GnRH administration to 29 patients caused a mean LH increase significantly less than that in normal men. Of the hyperprolactinemic men given CC, 6/10 exhibited a normal response, 1/10 showed an impaired response, and 3/10 did not respond; serum T and E2 increases were also significantly lower. MC did not elicit a significant increase in LH either in those with prolactinemia or in normal sub jects; PR did not rise in hyperprolactinemic men but did increase significantly in controls. Excess PRL apparently plays an inhibitory role in the hypothalamic-pituitary-testicular axis that seems to be related to the degree and duration of hyperprolactinemia. (27 Refs)

14. PLASMA CORTISOL RESPONSE TO EXOGENOUS ACTH IN 22 DOGS WITH HYPERADRENOCORTICISM CAUSED BY ADRENOCORTICAL NEOPLASIA.

Peterson ME, Gilbertson SR, Drucker WD
The Animal Medical Center, 510 E. 62nd St., New York, NY, 10021
J Am Vet Med Assoc; 180(5):542-544 1982

The plasma cortisol response to exogenous ACTH (ACTH stimulation test) was evaluated in 22 dogs with hyperadrenocorticism caused by adrenocortical neoplasia. The mean basal cortisol concentration (6.3 ug/dl) was high, but seven dogs had basal cortisol concentrations that were within normal range. Administration of exogenous ACTH increased the plasma cortisol concentrations in each dog. Normal post-ACTH cortisol concentrations were found in 9 (41%) of the 22 dogs; 13 (59%) had an exaggerated increase in cortisol concentrations after ACTH administration. In 9 of 13 dogs with carcinoma and in 4 of 9 with adenoma, the cortisol response was exaggerated. The mean post-ACTH cortisol concentration in the dogs with carcinoma was approx 4x that of the dogs with adenoma; the seven dogs with the highest concentrations h carcinoma. Repeat studies were performed in six dogs 2 to 8 wk after initial testing. In five of the six dogs, repeat testing yielded data of similar diagnostic significance. One dog, however, had an abnormally high post-ACTH cortisol concentration at initial evaluation, but had only a minimal response to ACTH administration, with a normal post-ACTH cortisol concentration, at time of retesting. Although ACTH stimulation testing is useful in diagnosing hyperadrenocorticism, it can not reliably separate dogs with hyperfunctional adrenocortical tumors from clinically normal dogs or from dogs with pituitary-dependent hyperadrenocorticism (bilateral adrenocortical hyperplasia). (Author abstract) (13 Refs)

15. SERUM SEX STEROID AND PEPTIDE HORMONE CONCENTRATIONS, AND ENDOMETRIAL ESTROGEN AND PROGESTIN RECEPTOR LEVELS DURING ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON.

Kauppila A, Cantell K, Janne O, Kokko E, Vihko R
Population Council, New York, NY
Int J Cancer; 29(3):291-294 1982

Five normally cycling healthy women were given daily sc injections of human leukocyte interferon (3 x 10(6) units/day) from the 3rd through 23rd day of the menstrual cycle, and serum steroid and peptide hormone concentrations monitored at 3-day intervals during the treatment and the preceding control cycle. Concentrations of cytosol and nuclear estrogen receptors (ERc and ERn, respectively) and progestin receptors (PRc and PRn) were also measured from endometrial biopsies taken on the 24th day of the control and treatment cycle. In addition, an extensive monitoring of clinical chemical and hematological tests from the blood samples were performed. Serum estradiol and progesterone concentrations were significantly decreased during the treatment cycle, suggesting that interferon interacts in vivo with the function of both FSH and LH. No significant changes were observed in the serum peptide hormone concentrations measured (FSH, LH, prolactin, insulin, growth hormone and TSH); neither were the levels of endometrial ERc, ERn, PRc and PRn affected by interferon administration. As expected, interferon administration resulted in decreased leukocyte counts. Moreover, an increasing tendency in the activities of serum alkaline phosphatase and gamma-glutamyltransferase during the interferon therapy shows that interferon may slightly interfere with the liver function. These results suggest that one of the mechanisms by which interferon treatment may affect the growth of hormone-dependent neoplasms could be the interaction with production and/or function of circulating hormonal compounds. (Author abstract) (15 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

16. OESTROGEN AND PROGESTERONE CYTOSOLIC RECEPTORS IN CLINICALLY INFLAMMATORY TUMOURS OF THE HUMAN BREAST.

Delarue JC, May-Levin F, Mouriesse H, Contesso G, Sancho-Garnier H

Unite de Biochemie Hormonale, Institut Gustav-Roussy, 94800 Villejuif, France

Br J Cancer; 44(6):911-916 1981

Estrogen (RE) and progesterone (RP) cytosolic receptors have been studied in 59 clinically inflammatory tumors of the human breast. The results were compared to those obtained in a series of 496 operable tumors. A single saturating dose of estradiol for RE and R5020 for RP was used and the cut-off between negative and positive tumors was 100 fmol/g tissue. A significant difference was seen (p less than 0.02) between the two classes of patients: (RE-, RP-) tumors were commoner among clinically inflammatory tumors (48%) than among operable ones (28%), independently of menopause. Concerning the histological type (based on an assessment of differentiation) and the histological grading there was a significant difference (p less than 0.001) between the two populations of tumors. No significant differences was found in the distribution of RE and RP among the three histological types, whereas a significant correlation existed between histological grading and RE (p less than 0.02). Finally, patients with RE clinically inflammatory tumors constitute a lower risk group, especially when they are free of metastases at the time of diagnosis. The presence of RE therefore seems to indicate, as in the operable tumor group, a favorable prognosis. (Author abstract) (34 Refs)

17. A NEW HUMAN CELL LINE DERIVED FROM A POORLY DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA.

Gal D, Forney JP, Dev VG, Porter JC
Dept. Obstetrics and Gynecology, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235
Gynecol Oncol; 13(1):50-57 1982

Establishment and characterization of an endometrial adenocarcinoma cell line are described. The tumor cells, designated AC-258, originated from a patient with a poorly differentiated adenocarcinoma of the endometrium. These cells have been passed in culture more than 102 times and have maintained their morphological and chromosomal integrity in a fashion suggestive of monocloning. Cells from passages 1, 58, and 102 were aneuploid. The av number of chromosomes per cell was 64.8, and 8-17 marker chromosomes per cell were identified and described. Histological evaluation of tumor explants from three passages grown in nude (athymic) mice revealed morphologic identity. The doubling time of AC-258 was 22 hr. No detectable estrogen- or progesterone-binding proteins were found. The AC-258 cell line provides researchers with another tool with which to investigate biochemical and biological properties of human cancer cells. (Author abstract) (12 Refs)

18. ABNORMAL GLUCOCORTICOID RECEPTOR IN ACUTE LEUKEMIA CELLS.

McCaffrey R, Lillquist A, Bell R
Section Medical Oncology, Boston Univ. Medical Center, 75 East Newton St., Boston, MA, 02218
Blood; 59(2):393-400 1982

In normal tissues, 3H-triamcinolone acetonide (3H-TA) labeled glucocorticoid receptors can be resolved into two components by DEAE chromatography: peak I elutes at 0.04 M salt and peak II at 0.22 M salt. By glycerol gradient centrifugation, peak I is 3.5S and peak II is 8.5S. Peak I binds to DNA, while peak II does not. Blast cell 3H-TA-binding macromolecules in 27 of 62 cases of acute leukemia had DEAE binding characteristics identical to those of normal tissues; the remaining 35 cases were abnormal. In these cases there was either a single DEAE species eluting in the peak I area (30 cases) or multiple low-amplitude peaks eluting across the entire gradient (5 cases). The abnormal single peak material failed to bind to DNA in five cases (of 5 studied), whereas peak I material from five cases (of 5 studied), showing normal peak I-peak II ratios, bound normally to DNA. In three cases (of 3 studied), the abnormal single peak material had a S value of 2-2.5S, whereas in five cases with normal peak I-peak II ratios, the S values were a 3.5S and 8.5S, respectively. We hypothesize that those leukemias with abnormal binder characteristics cannot respond to glucocorticoid therapy. (Author abstract) (27 Refs)

19. ESTROGEN RECEPTORS IN OVARIAN EPITHELIAL CARCINOMA.

Schwartz PE, LiVolsi VA, Hildreth N, Maclusky NJ, Naftolin FN, Eisenfeld AJ
Div. Gynecologic Oncology, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, C T, 06510
Obstet Gynecol; 59(2):229-238 1982

Specimens from 53% (16 of 30) of patients with untreated ovarian epithelial cancers between October 1976 and February 1979 had estrogen binding levels greater than 30 fmoles/mg of cytosol protein (receptor rich). The likelihood of a specimen being receptor rich appeared to be independent of patient age, histologic grade of tumor, clinical stage, and amount of residual tumor left after surgery. For 20 patients with previously untreated advanced disease a life-table analysis showed no significant difference when receptor-rich and -poor groups were compared in terms of either survival or time to first progression of disease. Analysis of more recent specimens (predominantly obtained after February 1979) indicates high-affinity binding of the estrogen consistent with receptor; occasional substantial heterogeneity in estrogen binding results between different sites of tumor involvement; and progestin-specific binding in some specimens. In an analogy to breast cancer, patients whose tumors are cytosol estrogen receptor rich might theoretically be responsive to the administration of antiestrogens. (Author abstract) (19 Refs)

20. INFLUENCE OF PROSTATIC SECRETION PROTEIN ON UPTAKE OF ANDROGEN-RECEPTOR COMPLEX IN PROSTATIC CELL NUCLEI.

Pousette A, Bjork P, Carlstrom K, Forsgren B, Hogberg B, Gustafsson JA
Dept. Medical Nutrition, Karolinska Institutet, S-104 01 Stockholm, Sweden
Prostate; 2(1):23-33 1981

The modulating effect of prostatic secretion protein (PSP) on the nuclear uptake of the androgen-receptor complex in the prostatic cell was investigated in vitro and the effects of estramustine on the cellular concentration of PSP were studied. PSP could be purified in sufficient quantities for further in vitro studies by chromatography on Concanavalin A. Addition of PSP decreased the amount of [3H]-R1881-receptor complex taken up by the prostatic cell nuclei by 10% to about 3% and decreased the retention of the [3H]-R1881-receptor complex on DNA cellulose from approx 25% of total androgen-receptor complex to about 3%. Castration and treatment with estradiol-17beta-valerate (2 mg/wk sc) led to drastic reductions in prostate wt and amounts of PSP/mg of total cytosolic protein. Administration of estramustine (1 mg/day im) resulted in a reduction of prostatic wt, but did not affect the amount of PSP/mg total cytosolic protein. Modulation of the concentration of PSP may be suitable for control of the effects of androgens on the prostate in a tissue-specific manner. Estramustine affects the prostate in a manner different from that of estrogens or castration. (21 Refs)

21. CORRELATION OF HISTOCHEMICAL AND BIOCHEMICAL ANALYSES OF ANDROGEN BINDING IN PROSTATIC CANCER: RELATION TO THERAPEUTIC RESPONSE.

Pertschuk LP, Rosenthal HE, Macchia RJ, Eisenberg KB, Feldman JG, Wax SH, Kim DS, Whitmore WF, Abrahams JI, Gaetjens E, Wise GJ, Herr HW, Karr JP, Murphy GP, Sandberg AA
Box 25, 450 Clarkson Ave., Brooklyn, NY, 11203
Cancer; 49(5):984-993 1982

A histochemical technique for the detection of androgen binding in prostatic cancer was performed on specimens from 108 patients and compared with a biochemical method in a double blind study of 77. Statistical analyses showed a significant agreement between the two assay systems for the qualitative and quantitative presence or absence of specific androgen binding, as well as for the subcellular localization of binding in nucleus and/or cytoplasm. Although the number of cases studied was too small for statistical analysis, there appeared to be good correlation between histochemical androgen binding results and clinical response, or lack of response to hormonal manipulation in 20 patients with Stage C and Stage D carcinoma. No correlation was evident between androgen binding and tumor grade or clinicopathologic stage of disease by either histochemistry or biochemistry. (Author abstract) (38 Refs)

22. STRUCTURAL SIMILARITY OF MOLYBDATE-STABILIZED STEROID RECEPTORS IN HUMAN BREAST TUMORS, UTERI AND LEUKOCYTES.

Niu EM, Neal RM, Pierce VK, Sherman MR
(c/o Sherman) Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Steroid Biochem; 15:1-10 1981

Effects of molybdate on the apparent quantity and/or structure of the cytosol receptors for progestins and estrogens in human breast tumors, progestins in benign and malignant uterine endometrium, and glucocorticoids in normal lymphocytes and leukemic cells were studied. Estrogen receptors (ER) were labeled with [6,7-3H]-estradiol, glucocorticoid receptors with [6,7-3H]-triamcinolone acetonide (TA), progestin receptors (PR) with [17alpha-methyl-3H]-promegestone (R5020), and serum corticoid-binding globulin with [4-14C]-cortisol. For kinetic studies, the control solutions (-Mo) were made 30 milli (m)M in KCl, so that they had the same conductivity as those containing 20 mM Na2MoO4 (Mo). In the -Mo samples labeled with R5020, the specific binding was max between 1 and 2.5 hr, but declined to 54% of this value by 6.5 hr. In the Mo samples labeled with either lower or higher progestin concentrations, at least 92% of the max binding persisted after 6.5 hr; indicating that molybdate inhibits many but not all of the receptor-degrading processes in breast tumor (BT) cytosols. Results of gel filtration of PR and ER in BT and uterine specimens indicated that all of these receptors appear to exist in the same discrete form in hypotonic Mo buffers, regardless of the class of steroid, species, tissue, or state of health or malignancy. Steroid-binding specificity and ultracentrifugal analyses of molybdate stabilized receptors showed that the significant inhibition of progestin binding to PR by the synthetic glucocorticoid TA paralle led the inhibition detected in unfractionated Mo cytosol. Comparison of molecular parameters indicated mol wt of approx 310,000, an axial ratio of 11, and that the molecular architecture of receptors is highly conserved in a wide range of mammalian tissues. (55 Refs)

23. SPONTANEOUS CANINE MAMMARY TUMORS: A MODEL FOR HUMAN ENDOCRINE THERAPY?

Raynaud JP, Cotard M, Andre F, Mialot JP, Rolland PH, Martin PM
Roussel-Uclaf, 75007 Paris, France
J Steroid Biochem; 15:201-207 1981

The possibility of the presence of estrogen (ER) and progestin receptors (PR) as markers for hormone-dependence in canine and in human mammary tumors (MT) was studied in an analysis of MT from 144 pet bitches. MT were analyzed for steroid hormone receptor (SHR) content and were submitted to pathological examination. No significant difference was noted in the prevalence of MT among different breeds, and SHR incidence did not vary significantly. SHR content was not related to age and its presence was similar in virgins and dams. The mean age of bitches with ER- and PR-positive tumors was 9.96 yr compared to 10.43 yr for the ER- and PR-negative group. Progestin treatment for contraceptive purposes had no significant effect on the incidence of SHR in MT. SHR were present more frequently in multinodular, than in single MT, and only 33% of all single MT had both ER and PR. MT were classified into three categories according to size of the tumor, but the incidence of SHR did not vary significantly among the groups. Incidence of ER and PR was quite similar in benign and malignant MT, but when present, the concentrations of either ER or PR tended to be higher in benign, than in malignant tumors. Benign epithelial and mixed tumors had similar incidence of ER and PR, approx 56%, while of all malignant MT 53% contained ER, 52% PR, and 44% both ER and PR. Results indicate that the canine MT could be an appropriate model for human breast cancer. (31 Refs)

24. IS A FUNCTIONAL ESTROGEN RECEPTOR ALWAYS REQUIRED FOR PROGESTERONE RECEPTOR INDUCTION IN BREAST CANCER?

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J Steroid Biochem; 15:209-217 1981

Presence of a functional estrogen receptor (ER) as a requirement for progesterone receptor (PR) induction in breast cancer (BC) was studied in the T47D human BC cell line. ER and PR were measured after 30 passages in modified medium. Cells had less than 0.04 picomole/mg DNA of specific, unfilled ER in the cytoplasm when measured on a sucrose gradient. ER are anomalous: 10 nanoM estradiol treatment failed to deplete and translocate cytoplasmic receptors, and nuclear receptors failed to be subsequently processed. ER of T47D cells also have an unusual response to the estrogen antagonist, nafoxidine, cell growth is not inhibited and minimal effects on PR were observed. PR are heat labile, sediment at 7-8S on sucrose gradients, and specifically bind progestins. After 0.1 uM progesterone treatment (PT) PR rapidly (1-2 min) move out of the cytoplasm and into the nuclei. One hr of PT depleted PR, and these were fully restored in 10-24 hr when progesterone was removed, indicating that the cells are either functionally ER-negative, or the ER are in a permanently activated state in the nucleus. Nafoxidine reverses this activated processed state. After 4 days on 20 ug/ml B-bromodeoxyuridine PR levels were reduced 70%. This effect was completely prevented by addition of excess thymidine (10x). When T47D cells were cultured in the presence of 10 milliM butyrate, PR levels fell 32% in 24 hr, and 55% in 36 hr. The inhibitory effect was completely reversible even after 72 hr, if the compound was removed from the medium. Results suggest that transcription of the PR gene in T47D cells is not constitutive, but remains at least partially regulated. (30 Refs)

25. THE PLASMA MEMBRANE AS AN ADDITIONAL LEVEL OF STEROID-CELL INTERACTION.

Nenci I, Fabris G, Marzola A, Marchetti E

Istituto di Anatomia e Istologia Patologica, Uni. Ferrara, 44100 Ferrara, Italy

J Steroid Biochem; 15:231-234 1981

The occurrence of sites of interaction additional to specific classical receptors is discussed with special regard to their possible role in the cell economy. Vital cell suspensions freshly obtained from human breast tumors without any enzymatic or chemical pretreatment were used as the target-cell substratum. The cell plasma membrane represents an additional level of steroid-cell interaction and the properties of the surface binding sites are in accordance with the belief that multiple binding sites for steroid hormones occur in target cells. (12 Refs)

26. SPECIFIC PROTEIN SYNTHESIS REGULATED BY ESTROGEN IN HUMAN BREAST CANCER.

Edwards DP, Adams DJ, McGuire WL
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J Steroid Biochem; 15:247-259 1981

Specific protein synthesis regulated by estrogen was studied in MCF-7 human breast cancer cells. Results for effects of estradiol on the pattern in protein synthesis, specificity of antiestrogen pretreatment, time course, estrogen dose response and hormone specificity of 24,000 mol wt (24k) stimulation, relationship between nuclear estrogen receptors and 24k stimulation, identity of 24k protein, two-dimensional electrophoresis, and estradiol stimulation of specific messenger RNA activity, are presented. Results indicate that specific proteins stimulated by estrogen in MCF-7 cells may prove to be suitable markers to study whether estrogens regulate expression of specific genes in breast cancer cells. (43 Refs)

27. GLUCOCORTICOID RECEPTOR STUDIES IN HUMAN LEUKEMIA.

Marchetti P, Natoli V, Raneletti FO, Mandelli F, De Rossi G, Iacobelli S
Lab. Molecular Endocrinology, S. Cuore Catholic Univ., 00100 Rome, Italy
J Steroid Biochem; 15:261-268 1981

Glucocorticoid receptors (GR) and glutamine synthetase (GS) activity were measured in leukocytes from peripheral blood of patients with acute lymphoblastic leukemia (ALL). Problems in GR determination, results for GR and response to glucocorticoid treatment and chemotherapy, and presence and inducibility of GS in ALL cells, are discussed. GR density in leukemic lymphoblasts in ALL correlates positively with the short-term response in glucocorticoid treatment and with the inducibility of complete remission, independent of other prognostic factors. (54 Refs)

28. IN VITRO GLUCOCORTICOID STUDIES IN HUMAN LYMPHOMA: CLINICAL AND BIOLOGIC SIGNIFICANCE.

Bloomfield CD, Smith KA, Peterson BA, Gajl-Peczalska KJ, Munck AU
Univ. Minnesota Hospitals, Box 277, Minneapolis, MN, 55455
J Steroid Biochem; 15:275-284 1981

Results from summarized studies of receptor levels from tumor cells from different tissues, in vitro glucocorticoid (GC) assays in control lymph nodes and in lymphoma, in vitro GC assays and response to GC therapy, effect of in vivo GC administration on receptor levels, and sequential studies of tumor receptors at diagnosis and relapse, on patients and volunteers, are presented. Receptor levels in tumor cells from different sites did not correlate well and since sufficient numbers of lymphoma cells (LC) from marrow and blood are available in less than 25% of patients, LC from lymph nodes were used. Median number of GC receptor sites/cell were 691 for cytoplasmic receptors, 1,481 for nodular, and 2,085 for total receptors. Inhibition of leucine incorporation by dexamethasone (DM) was significantly greater in lymphomas than in control lymph nodes. Significant differences between responders and nonresponders were not seen in DM inhibition of radiolabeled leucine or thymidine incorporation. No pretreatment clinical characteristics could be used to predict those patients who would respond to GC therapy. The fall in receptor numbers following GC administration could be explained as intrinsic regulation by the cell of receptors in response to in vivo changes in hormone (GC) level (down regulation). Data suggest that following relapse, cases initially sensitive to GC may develop resistance by selection of cells with fewer receptors, and administration of DM to patients may result in selection of lymphoma cells with lower number of receptors. Chemotherapy in addition to GC may accelerate the process. (27 Refs)

29. HORMONE BINDING OF ESTRADIOL-17BETA RECEPTOR: EVIDENCE FOR ITS REGULATION BY CYTOPLASMIC PHOSPHORYLATION AND NUCLEAR DEPHOSPHORYLATION. PREVENTION OF DEPHOSPHORYLATION BY ANTIESTROGENS.

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J Steroid Biochem; 15:369-373 1981

Hormone binding activity of estradiol-17beta receptors was studied and evidence for its regulation by cytoplasmic phosphorylation and nuclear dephosphorylation is presented. The high affinity of the nuclear phosphatase for the inactivated estradiol receptor supports the possibility that this cytosol enzyme has a physiological role. The enzyme could phosphorylate newly synthesized receptor, making the protein able to bind estradiol-17beta and to migrate into nuclei, and could also recycle at least a part of receptor inactivated by nuclear phosphatase in the nuclear compartment. (11 Refs)

30. THE EFFECTS OF A SECOND SPECIFIC ESTROGEN BINDING SITE ON ESTROGEN RECEPTOR QUANTITATION IN HUMAN BREAST CANCER CYTOSOL.

Panko WB, Clark JH
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 15:383-386 1981

The quantity of estrogen receptors (ER) in five pools of human breast cancer (HBC) tissue was determined by saturation analysis over a full or abbreviated range of ligand concentrations to determine how much type II estrogen binding site (II EBS) might affect the quantitation of ER in HBC cytosol. Results indicate that saturation analysis (SA) over a wide range of ligand values is an acceptable method to quantitate ER accurately. SA over a limited range of ligand concentrations does not allow the resolution or even detection of two-component binding systems. Use of a dextran-coated charcoal-based analytical system may not afford protection against error since it does not completely strip ligand from II ESB at a ligand concentration of 40 nanoM. (15 Refs)

31. STEROID STRUCTURE AND NUCLEAR TRANSLOCATION OF GLUCOCORTICOID RECEPTORS IN INTACT ATT-20 MOUSE PITUITARY TUMOR CELLS.

Harrison RW, Miyabe S
Div. Endocrinology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
J Steroid Biochem; 15:393-396 1981

The degree of in vivo activation caused by glucocorticoids (triamcinolone acetonide, dexamethasone, prednisolone, corticosterone) was determined in intact AtT-20 mouse pituitary tumor cells and the relationship between the degree of activation and extent of nuclear translocation was investigated. Determination of the total amount of activated receptor within the cell revealed a linear correlation between extent of nuclear binding caused by each steroid and the proportion of activated receptor. (7 Refs)

32. NUCLEAR ANDROGEN RECEPTOR AS MARKER OF RESPONSIVENESS TO MEDROXYPROGESTERONE ACETATE IN HUMAN RENAL CELL CARCINOMA.

Concolino G, Marocchi A, Toscano V, Di Silverio F
Istituto di Clinica Medica Generale e Terapia Medica V, Universita di Roma, Roma , Italy
J Steroid Biochem; 15:397-402 1981

Androgen receptors (AR) were measured in the cytoplasmic and nuclear fractions of human renal cell carcinoma (RCC) in order to find a parameter (ARn) which could better predict the response to hormonal therapy. Cytosol AR were detected in 50% and ARn in 57% of the tumors examined. AR do not only help to define the hormone-dependent human RCC, but may also be useful in the selection of patients to be treated with medroxyprogesterone acetate (MPCA). MPCA could counteract the promoting action of estrogens on tumor growth only in patients with ARn positive tumor. (27 Refs)

33. ESTROGEN REGULATION OF RAT PROSTATE ANDROGEN RECEPTOR.

Bouton MM, Pornin C, Grandadam JA
Centre de Recherches Roussel-UCLAF, 93230 Romainville, France
J Steroid Biochem; 15:403-408 1981

Estrogen regulation of rat prostate androgen receptor (AR) was studied. Results for effects of estrogen on cytosol AR and of anti-estrogen treatment on the estrogen-induced increase in cytosol AR, and cytosolic estrogen receptor (ER) in rat prostate are presented. Estrogens which do not interact with AR (moxestrol, diethylstilbestrol, ethynyl estradiol) are also able to increase cytosolic AR and the increase might be mediated by the ER present. (36 Refs)

34. EFFECT OF THYROID HORMONES ON ANDROGEN RESPONSIVENESS IN A MAMMARY TUMOR CELL LINE.

Sica G, Natoli C, Marchetti P, Iacobelli S
Istituto di Istologia ed Embriologia Generale, Universita Cattolica del Sacro Cuore, Largo Gemelli 8, 00168 Roma, Italy
J Steroid Biochem; 15:415-419 1981

Effects of thyroid hormones (TH) on androgen responsiveness (AR) were studied in Shionogi mouse mammary carcinoma cells (S115) and the variability of hormone response and duration of endocrine-induced remissions in human cancer regressions was investigated. Triiodothyronine (T3) at physiological concentrations slows down the loss of AR in S115 cells, cultured in the absence of testosterone. This is not mediated by the androgen receptor, since its level remains constant. T3 effect is more evident in the presence of AG1 x 10 anion-exchange resin which depletes serum of TH. (15 Refs)

35. GLUCOCORTICOID RECEPTORS AND HORMONAL RESPONSIVENESS OF HUMAN BLOOD AND BONE-MARROW CELLS IN NON-LYMPHOCYTIC LEUKEMIA.

Homo F, Durant S, Duval D, Marie JP, Zittoun R, Harousseau JL
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J Steroid Biochem; 15:479-485 1981

Glucocorticoid receptors (GR) and hormonal responsiveness of human blood and bone-marrow cells in non-lymphocytic leukemia were studied. Results for determination of GR, comparison of the drug effect on nucleoside incorporation by blood and bone-marrow samples, and cell heterogeneity and the variability of drug effects of subpopulations isolated by gradient centrifugation, are presented. Correlation between the number of binding sites and the in vitro or in vivo response to glucocorticoids could not be established, suggesting that the experimental conditions do not correspond to the in vivo situation. Prostaglandin markedly enhanced the level of [3H]-thymidine incorporation in the patients tested. (29 Refs)

36. PROGESTERONE THERAPY RESULTS IN PARTIAL REVERSIBILITY OF UTERINE ABNORMALITIES OF THE ADULT ANOVULATORY RAT.

White JO, Moore PA, Elder MG, Lim L
Inst. Obstetrics and Gynecology, Hammersmith Hosp., Du Cane Road, London W12 0HS, England
Biochem J; 202(2):535-541 1982

The effects of progesterone therapy (5 mg, administered sc daily for 6 days) on the abnormal uterus of adult anovulatory Wistar rats have been studied. These rats, rendered anovulatory by neonatal treatment with testosterone propionate or clomiphene citrate, displayed severe hyperplasia and metaplasia of the uterine luminal epithelium and a disproportionately high content of nuclear estrogen receptor, as a result of constant estrogen stimulation unrelieved by progesterone. Progesterone therapy resulted in the virtual elimination of the hyperplasia and metaplasia and a corresponding decrease in the content of nuclear estrogen receptor with the proportion of the unoccupied nuclear receptor being increased to values exhibited by normal cyclic females. There was also a decrease in the content of progestin receptors, a putative index of estrogenic stimulation. Further, in the testosterone-treated group, progesterone therapy resulted in the restoration of estrogen receptor translocational responses to estradiol stimulation. Progesterone treatment of these anovulatory rats thus provides a model system for investigating the biochemical mechanisms underlying progestin antagonism and regulation of estrogen-stimulated cell proliferation. (Author abstract) (40 Refs)

37. AN ALTERNATIVE APPROACH TO THE QUANTITATION OF GLUCOCORTICOID-RECEPTOR COMPLEXES IN THE NUCLEI OF LYMPHOID CELLS.

Kaufmann SH, Quddus FF, Shaper JH
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Endocrinology; 110(3):708-716 1982

We have developed a rapid and convenient method for the quantitative assessment of nuclear translocation of glucocorticoid-receptor complexes in lymphoid cells. In this assay, cells are incubated with [3H]dexamethasone at 4 C or 21 C, treated for 15 min at 4 C with the sulfhydryl blocking reagent sodium tetrathionate or methyl methanethiolsulfonate, and then ruptured with the neutral detergent Triton X-100 to separate the nuclei from the cytoplasmic constituents. When cells are incubated with [3H]dexamethasone at 21 C, an av of 45-60% of the specifically bound cellular radiolabel remains with the nuclei. In contrast, less than 15% of the hormone remains with the nuclei when cells are labeled at 4 C. In rat thymocytes, quantitatively similar results were obtained using this new method and a conventional method of isolating nuclei (homogenization of cells in a hypotonic buffer). For both methods, preincubation of the labeled cells with the sulfhydryl blocking reagents was essential to prevent release of the nuclear hormone (or hormone-receptor complex) by a sulfhydryl-dependent labilizing activity apparently located in the cytoplasm. The new method has been successfully used to quantitate uptake of nuclear [3H]dexamethasone-receptor complexes in rat thymocytes, human lymphocytes, and human leukemia cells of lymphoid and myeloid origin. It should prove successful for separating nuclear from cytoplasmic glucocorticoid-receptor complexes in a wide variety of cells, many of which resist disruption by more conventional techniques. (Author abstract) (49 Refs)

38. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER FED ALPHA-NAPHTHOFLAVONE.

Li SA, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Steroid Biochem.; 15:387-392 1981

Incidence of hepatocarcinogenesis was investigated in diethylstilbestrol (DES)-treated castrated and ovariectomized Syrian golden hamsters fed 0.2% alpha-naphthoflavone (ANF) in the diet. Induction of liver tumors (LT) by DES was essentially nil. When similar DES-treated castrated male hamsters were maintained on a diet containing ANF, nearly 70% developed LT. No LT were found in hamsters treated with ANF alone. Diet containing beta-naphthoflavone alone, or in the presence of DES did not induce LT. Competition with 250-fold excess nonlabeled DES for tritiated estradiol (ED) binding indicated that only the 8S moiety of estrogen receptors (ER) was specific. The specificity of ER in cytosol was indicated by minimal inhibition when either radioinert cortisol, progesterone, methyltrienolone, or triamcinolone acetonide was used at the same concentration. The binding of [3H]-ED in DES plus ANF-treated liver cytosol was saturable and of high affinity with an association constant of 0.15-1.3 x 10(9) M-1. Similar results were obtained using liver cytosol derived from untreated castrated and DES-treated hamsters. DES treatment for 3-4 mo resulted in a 2.5-fold increase in specific estrogen binding, and treatment with DES plus ANF for a similar period induced a 3.5-5-fold increase in liver ER concentration. In both treated groups when sedimented in high salt sucrose gradients, 4S nuclear binders were detected for liver ER. Cytosol-nuclear receptor translocations carried out either in the presence of nonlabeled DES or at 0-3 C exhibited little nuclear uptake of the labeled ED in all tissues examined. (37 Refs)

39. ALTERATIONS IN THE GENE EXPRESSION IN TUMORS.

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Lijec Vjesn; 103(4/5):201-203 1981

Alterations of gene expression in tumors are discussed. Relationship of cytoplasmic (ERc) and nuclear estrogen receptors (ERn) and progesterone receptors (PgR) in human breast cancer was studied in 97 females patients. PgR were correlated with the presence of ERn in more than 80% of the cases. Presence or absence of ERc had no influence on PgR. Significant correlation was observed between ERn and PgR, but no correlation was observed between these receptors and ERc. Presence of PgR in some ERn negative (ERn-) tumors indicates the possibility that PgR synthesis does not depend on the induction. Various combinations of receptors were observed in the studied tumors. In the ERc positive (ERc) group some of the tumors contained no ERn. Levels of endogenous estradiol appeared sufficient to induce PgR and the translocation of ERn and ERc. Forty percent of ERc tumors are nonresponsive to hormonal therapy. Eleven percent of ERc- tumors contain ERc-, ERn, and PgR, and they are responsive to hormonal therapy. Determination of ERn in the cell nuclei of breast cancer could help in identification of hormone resistant tumors with no ERc and defect mechanisms for receptor translocation. (24 Refs) (In SCR)

40. STEROID RECEPTORS IN MAMMARY CANCER.

Stojkovic RR
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Libri Oncol; 10(2/3):313-316 1981

Steroid receptors were determined in 500 patients with mammary cancer (MC). Primary MC was found in 434 patients, and 66 had metastasizing (ME) MC. Results of estrogen receptors in cytoplasm (ERc) were positive in 232 patients with primary MC and in 30 with ME MC. ERc and progesterone receptors (PgR) were determined in 315 patients, 33% of the patients had both ERc and PgR. Twenty-one percent of the patients had ERc only, while 14% had PgR only. Number of tumors containing PgR increases with increasing amount of ERc. The amount of ERc was increasing with the age of the patients. PgR in ERc tumors was approx the same before or after the menopause. ERc, PgR, and estrogen receptors in nucleus (ERn) were determined in the 97 MC patients. ERn was found in 37% of the patients, increasing to 66% in ERc. If ERc and ERn were positive, PgR was found in 90% of the patients; but when ERc was negative and ERn positive, PgR was found in 83%; when both (ERc and ERn) were negative, PgR was found in only 18% of the patients. Number of tumors containing PgR increases with increasing amount of ERc without relationship in their amounts, while amounts of PgR and ERn were significantly and positively correlated. Possible relationship of the three steroid receptors and success of hormonal therapy were discussed. (14 Refs) (In SCR)

41. STEROID RECEPTORS AS PROGNOSTIC INDICATORS IN PATIENTS WITH MAMMARY CANCER.

Bulic N, Budisic Z, Naranck P, Stojkovic R, Kubovic M, Gamulin S, Kosovel E, Martinac P, Montani Dj, Unusic J
Zavod za klinicku onkologiju i radioterapiju, Medicinski fakultet Sveucilista u Zagrebu, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):317-321 1981

Estrogen receptors (ER) and progesterone receptors (PgR) were determined in 205 patients with mammary carcinoma. Twenty one percent of the patients were in Stage I, 61% in Stage II, and 18% in Stage III. Possible response to therapy was rated R for the patients with tumors containing ER greater than 100 femtomoles (fmol)/mg protein (pr) or ER greater than 3 fmol/mgpr and with PgR greater than 20 fmol/mgpr, R for the patients with ER between 3-100 fmol/mgpr, and PgR- or ER- and PgR greater than 20 fmol/mgpr, and R- for the remaining patients. The 113 patients in Stage I and in Stage II were evaluated for 18 mo after surgery; of the 36 patients rated R none had relapse; of the 20 patients rated R, 8/20 had relapse, and three of them died; and of 57 rated R-, 12/57 had relapse, and 5 of them died. The 94 patients in Stage I and Stage II were evaluated for 24 mo after surgery; of the 25 patients rated R, 2 had relapse, and 1 of them died; of the 19 patients rated R, 9 had relapse, and 3 of them died; and of the 50 patients rated R-, 17 had relapse, and 9 of them died. Discrepancy in results between R and R- could be due to adjuvant chemotherapy administered in higher percentage to the patients rated R-. Patients with low or negative values of the steroid receptors should be considered at high risk. (11 Refs) (In SCR)

42. ESTROGEN RECEPTORS AND RESPONSE TO CHEMOTHERAPY IN ADVANCED BREAST CANCER.

Cocconi G, De Lisi V, Mori P, Bozzetti C
Servizio di Oncologia Medica, Ospedali Riuniti, Via Gramsci 14, 43100 Parma, Italy
Tumori; 68(1):67-71 1982

The relationship between receptor status and response to combination chemotherapy was retrospectively analyzed in 50 patients with advanced breast carcinoma, previously untreated with systemic therapy. Overall objective response rate to combination chemotherapy was similar in ER cases (14 of 33, 42%) and in ER- (9 of 17, 53%). The median duration of response was significantly longer in ER cases (48 wk) than in ER- ones (26 wk, p = 0.03). Response rate to cytotoxic chemotherapy does not appear to correlate with ER status. (Author abstract) (35 Refs)

43. SITE-SELECTIVE GROWTH OF A HORMONE-RESPONSIVE HUMAN BREAST CARCINOMA IN ATHYMIC MICE.

White AC, Levy JA, McGrath CM
Dept. Tumor Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 42(3):906-912 1982

MCF-7 is a human breast cancer line which requires estradiol supplementation for growth in sc tissues of athymic mice. In order to evaluate the influence of host site on hormone-dependent tumorigenicity and growth, MCF-7 cells were inoculated into tissues varying in ability to concentrate exogenous estradiol. Tumorigenicity was defined in terms of latency, threshold inoculum size, and tumor growth and progression. We observed that sites such as lung rarely supported MCF-7 tumors. However, moderately estrophilic sites such as mammary fat and adjacent subcutaneum and dermis supported the growth of small MCF-7 tumors from large tumor cell inocula, but only in estrogenized mice. In contrast, the highly estrophilic sites, brain and periuterine tissues, produced rapidly growing tumors from small cell inocula. Only in periuterine tissues did tumors develop in the absence of exogenous estradiol. These studies demonstrate that tumorigenicity and growth rates of estrogen-dependent MCF-7 tumors vary as a function of tissue implantation site. (Author abstract) (46 Refs)

44. EFFECTS OF ESTROGENS ON ARYL HYDROCARBON HYDROXYLASE MEDIATED BINDING OF BENZO(A)PYRENE METABOLITES TO DNA IN VITRO.

Williams MT, Hendley R
Dept. Biochemistry, Coll. Medicine, Univ. South Florida, Tampa, FL, 33612
Biochem Biophys Res Commun; 104(4):1349-1355 1982

Liver microsomes from mice injected with 0.1 or 2 mg of estradiol (ES) 24 prior to, during and 24 hr after injection of 3-methylcholanthrene (MC), exhibited a significantly decreased capacity to mediate the binding of benzo(a)pyrene metabolites to DNA, compared to microsomes from mice which received only MC. The enzyme and cytochrome components of the aryl hydrocarbon hydroxylase (AHH) were not affected by either ES treatment, suggesting ES may act as a non-competitive inhibitor of AHH activity. (20 Refs)

45. STUDIES ON NUCLEAR ESTRADIOL RECEPTORS IN HUMAN MAMMARY CARCINOMAS.

O'Connell M, McDonnell L, Duffy MJ
(c/o Duffy) Nuclear Medicine Dept., St. Vincent's Hosp., Dublin 4, Ireland
Clin Chim Acta; 119(3):285-289 1982

It is known that 50-70% of human primary mammary carcinomas possess cytoplasmic estradiol receptors (CER) and that over 5x as many CER- as non-CER-carcinomas respond to hormone manipulative therapy. This study demonstrates that 59% of CER- and 24% of non-CER carcinomas possess nuclear estradiol receptors (NER), whose presence should be a better indicator of amenability to this therapy. The correlation between CER and NER is r = 0.55 (p = 0.0001, n = 92). NER does not correlate with tumor cellularity, size, histological type, presence/absence of axillary node metastases, or cytosol levels of either total estrogens or progesterone. Presence or absence of NER does not alter the total cytosol estrogens median or the cytosol progesterone mean level. The percentage of tumors with over 25 fmol NER receptor/g wet weight decreases as the histologic tumor grade or stage increases, but not in a statistically significant manner. The significance of these findings is discussed in relation to recent literature on NER and CER, and rests upon results of ongoing clinical studies. (13 Refs)

46. GLUCOCORTICOID RECEPTORS IN LEUKEMIC CELLS OF CHILDREN WITH ACUTE LEUKEMIA.

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Dept. Pediatrics, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 31(1):109-125 1981

Levels of glucocorticoid receptors (GCR) in leukemic cells in children with acute leukemia were measured. Blood samples were obtained from 80 patients (41 males and 39 females, 2 mo-22 yr old). Cases included 65 of acute lymphoblastic leukemia (ALL) and 15 of acute myeloblastic leukemia (AML). Binding of [3H]dexamethasone (DMS) was measured with whole cells and with cytosol fractions. Nuclear binding accounted for 60%, cytosol binding for 40%, of total binding. Nuclear binding was proportional to cytosol binding and did not become saturated at DMS levels sufficient to saturate cytosol binding. With DMS levels sufficient to saturate GCR, equilibrium was approached after 90 min. GCR levels, in sites/cell, were 2,827-90,300 (mean 30,039) for patients with ALL and 2,348-40,936 (mean 14,207) for patients with AML. Normal lymphocytes had 1,926-11,438 (mean 6,620) sites/cell. Among patients with ALL GCR levels for 13 patients showing good response to glucocorticoid therapy were 15,050-90,300 (mean 45,451, median 32,508); for 7 patients relapsing within 1 yr 7,525-58,996 (mean 28,233, median 24,682); for 14 poor responders 2,227-22,876 (mean 7,765, median 4,816). Differences between good responders and poor responder were significant; differences between good responders and early relapsers were not significant. GRC levels can apparently be used to predict, to some extent, response to glucocorticoid therapy in patients with ALL, but not to predict duration of remission. (30 Refs)

47. FAILURE OF PROGESTINS TO INDUCE ESTRADIOL DEHYDROGENASE ACTIVITY IN ENDOMETRIAL CARCINOMA, IN VITRO.

Satyaswaroop PG, Mortel R
Div. Gynecologic Oncology, Dept. Obstetrics and Gynecology, Milton S. Hershey Medical Center, Hershey, PA, 17033
Cancer Res; 42(4):1322-1325 1982

Estradiol dehydrogenase (E2DH) is a well-known progesterone-dependent enzyme in human endometrium, and its induction has been proposed as a means to test hormonal sensitivity of endometrial carcinoma. While administration of progestins to some patients with endometrial carcinoma resulted in increased endometrial E2DH activity, efforts to induce this enzyme, in vitro, in these tumors have been unsuccessful. The reasons for such failure were investigated in the present study. Progesterone receptor (PR) concentrations and E2DH activities were simultaneously measured in proliferative and malignant endometria under organ culture conditions. Cytoplasmic PR concentrations were determined by Scatchard plot analysis of [3H]progesterone binding in fresh samples and in tissue explants incubated in nutrient medium at 37 C in a humidified 5% CO2 atmosphere for various periods of time. Parallel incubations of explants with and without 500 ng medroxyprogesterone acetate per ml were carried out for monitoring E2DH induction. In proliferative endometrium, the progesterone-specific binding sites remained stable during the culture periods, and the E2DH activities were stimulated severalfold by medroxyprogesterone acetate. In contrast, the PR concentrations in carcinoma explants were undetectable after a 24-hr period, and this was associated with a lack of increase in E2DH activity. These findings provide evidence that progestin-induced endometrial E2DH activity is a receptor-mediated phenomenon. In addition, these results demonstrate clearly that the ineffectiveness of progestin to induce E2DH in endometrial cancer specimens, in vitro, is related to the instability of PR under culture conditions. It is suggested that any experiment designed to follow effects of steroids on target tissues must take into account the stability of steroid receptors under in vitro conditions. (Author abstract) (22 Refs)

48. THREE RADIOLIGANDS COMPARED FOR DETERMINING CYTOPLASMIC ESTROGEN-RECEPTOR CONTENT OF HUMAN BREAST CARCINOMAS.

Pieslor PC, Gibson RE, Eckelman WC, Oates KK, Cook B, Reba RC
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Clin Chem; 28(3):532-537 1982

We compared three radioligands for use in a cytoplasmic estrogen-receptor assay, using pooled cytosol from human breast adenocarcinomas. The estrogen receptor content was determined in vitro by a dextran-coated charcoal method involving a 4-hr incubation with and without diethylstilbestrol. Tritiated moxestrol failed to come to equilibrium in 4 hr, thereby preventing the use of conventional one-component Scatchard analysis. The use of 125I-labeled estradiol resulted in a higher estimate of estrogen-receptor concentration than that obtained with use of tritiated estradiol. This overestimation was not corrected by Scatchard, double-reciprocal, or Woolf plots, or by two different methods of data analysis: least squares and 'robust.' An underestimation of the specific activity of iodoestradiol with respect to that of tritiated estradiol and an unrecognized second component of nonreceptor binding could explain this disparity. (Author abstract) (24 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

49. STRUCTURAL FORMS OF CARCINOGENESIS IN THE PORTIO-CERVIX REGION UNDER THE INFLUENCE OF EXOGENOUS HORMONES.

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Pathologe; 3(1):13-24 1981

A possible relationship between the use of exogenous hormones (eg, oral contraceptives or gestagen therapy) and the development of cancerous and precancerous lesions in the uterine cervix is discussed. The effects of estrogens and gestagens on the epithelium of the portio and cervical mucosa are described, and early stages of epithelial hyperplasia are detailed. Malignant development of regeneration epithelium of the portio and reserve epithelium of the cervix is outlined, with emphasis on the effects of exogenous hormones. Histological characteristics are detailed for the following precancerous and cancerous lesions: dysplasia, carcinoma in situ, microcarcinoma, invasive squamous cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, and adenocarcinoma. The development of the latter type of malignancy from atypical adenomatous hyperplasia and adenocarcinoma in situ is examined in detail; the effects of hormones are considered. It is concluded that, while no direct relationship between hormone administration and development of squamous cell carcinoma has been established, there is substantial evidence of such a relationship between hormone administration and the development of adenocarcinoma of the cervical mucosa. (26 Refs) (In GER)

50. ASSESSMENT OF OESTROGEN AND PROGESTIN EFFECTS ON EPITHELIUM AND STROMA FROM PRE- AND POSTMENOPAUSAL ENDOMETRIUM.

King RJ, Lane G, Siddle N, Taylor RW, Townsend PT, Whitehead MI
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J Steroid Biochem; 15:175-181 1981

Efficacy of commercially available progestin preparations were investigated to determine the optimum type, dose, duration, and route of administration required to protect the endometrium. Biochemical indices of estrogen and progestin action of endometria from menopausal women receiving various hormone therapies given by different routes were monitored. Premenopausal samples obtained during the proliferative and secretory phases of the cycle have also been analyzed so that the degree of hormonal stimulation of the postmenopausal endometria can be compared with physiologically normal activities. Results obtained are discussed with respect to the formulation of hormone therapy for postmenopausal women that relieves the symptoms of estrogen deficiency yet minimize the risk of estrogen-related endometrial carcinoma and progestin-related cardiovascular changes. (28 Refs)

51. THE INFLUENCE OF ANDROGENS, ANTI-ANDROGENS, AND CASTRATION ON CELL PROLIFERATION IN THE JEJUNAL AND COLONIC CRYPT EPITHELIA, AND IN DIMETHYLHYDRAZINE-INDUCED ADENOCARCINOMA OF RAT COLON.

Tutton PJ, Barkla DH
Dept. Anatomy, Monash Univ., Clayton, 3168, Australia
Virchows Arch [Cell Pathol]; 38(3):351-355 1982

Androgenic hormones have previously been shown to promote cell proliferation in the small intestine of rat and androgen receptors have been demonstrated in carcinomata of the large intestine of rat. In this study the influence of testosterone and of castration on epithelial cell proliferation in the small intestine, the large intestine and in dimethylhydrazine-induced colonic tumors is compared. Cell proliferation in the small intestine and in colonic tumors was accelerated by testosterone treatment, and cell proliferation in colonic tumors, but not in the small intestine, was retarded following castration. Cell proliferation in colonic tumors was also inhibited by the anti-androgenic drug, Flutamide. Testosterone and castration each failed to influence cell proliferation in the colonic crypt epithelium of both normal and carcinogen-treated animals. (Author abstract) (22 Refs)

52. THE EFFECT OF LH1, AN AMINOACYL-STEROID, ON CULTURED HEPATOMA CELLS.

Giesen EM, Beck JP, Beck G, Nguyen-Dang T
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Cancer Biochem Biophys; 5(4):233-238 1981

LH1, synthesized from 3alpha-amino-5-alpha-pregnane-20-one and N-protected glycine, was used in experiments on HTC cells from clone 7288C of Morris hepatoma in the rat. LH1 penetrated rapidly into cells, at a rate comparable to that of dexamethasone. LH1 exerted a powerful cytoxic effect on HTC cells: half maximal growth inhibition after 1 day was obtained at 15 ug/ml, and after 3 days at 6 ug/ml; 53 ug/ml killed all cells after 1 day, and 30 ug/ml killed all cells after 2-3 days. Logarithmically growing cells were more sensitive than quiescent cells. DNA and RNA synthesis, measured by (3H)thymidine and (3H)uridine incorporation, respectively, were inhibited reversibly below a threshold concentration of 30 ug LH1/ml of cell suspension. LH1 has even more severe inhibitory effects on protein synthesis, and the threshold concentration is lower, suggesting that DNA and RNA synthesis effects may be secondary (low LH1 concentration) or due to a different mechanism of action (high LH1 concentration). (14 Refs)

53. EFFECTS OF STEROIDS ON VIRAL INFECTION OF HUMAN BREAST CANCER CELL LINES BY ADENOVIRUS 5.

Chouvet C, Chardonnet Y, Saez S
Centre Leon Berard, 28 rue Laennec, 69372 Lyon Cedex 2, France
J Steroid Biochem; 15:269-274 1981

Effects of steroid hormones, especially estradiol (ES), on the infection of MCF7, a human epithelial cell line established from a metastatic breast adenocarcinoma, by adenovirus 5 were studied. Cytopathy induced by viral infection occurred 24 hr earlier in the presence of 10(-8) M ES. Some differences in the synthesis of viral proteins were detectable at 32 hr, and at 40 hr 78% of cells grown in the presence of hormone were positive vs 44% in the control. Potentiation of viral production is significant after 29 hr of infection and is max from 37 to 48 hr. The quantity of complete infectious particles produced in the control without hormone was very small for low virus concentrations [10 plaque forming units (PFU)/ cell] and increased with the dose of virus used. In the presence of ES, the difference with control was max for low infectious doses. Cells infected in the presence of 10(-9) M ES did not produce more viral particles than controls, but the addition of 10(-8) M ES amplified the number of PFU produced/cell approx 10x. Hormone deletion after infection did not decrease the production of viral particles. Whether the hormone was deleted for 2 or 4 hr before infection, the increase in viral production occurred as if hormone were present. The hormonal effect is apparently steroid specific and requires the corresponding receptors. More viral DNA is synthesized in the presence of hormone and max effect occurs later in the presence of hormone. No evidence was obtained for the synthesis of a protein specific to the hormonal effect, but the kinetics of synthesis were different between the hormone treated and untreated cultures. (26 Refs)

54. ESTROGEN-INDUCED SYNTHESIS AND SECRETION OF PROTEINS IN THE HUMAN BREAST CANCER CELL LINE MCF-7.

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J Steroid Biochem; 15:375-381 1981

Estrogen-induced synthesis and secretion of proteins (IP) were studied in the human breast cancer cell line MCF-7, the association of creatine kinase activity with IP fraction was tested, and the potential relationship of IP with cytosolic and secreted proteins was investigated and results compared with other studies. IP was resolved into two major proteins of 52,000 and 46,000 mol wt and two minor ones of 54,000 and 60,000 mol wt. Estradiol stimulated within 2 hr the synthesis of the four proteins in the responsive MCF-7 cell line, but not in the Evsa-T cells which lack the estrogen receptors. (23 Refs)

55. INTERACTION OF PROLACTIN, ESTROGEN AND PROGESTERONE IN A HUMAN MAMMARY CARCINOMA CELL LINE, CAMA-1. I. CELL GROWTH AND THYMIDINE UPTAKE.

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J Steroid Biochem; 15:421-427 1981

The growth and thymidine (TDR) uptake of a human mammary carcinoma cell line (CAMA-1) in long term monolayer culture were investigated. The cells were maintained in the log phase for 7 days in Eagles' minimum essential medium with Earle's salt, supplemented with 15 or 25% fetal bovine serum (FBS) without further feeding. The effects of FBS, dextran-charcoal treated FBS (DCFBS), and serum substitute (SS) were investigated. CAMA-1 cells grew poorly in SS as compared to 25% FBS. With addition of either 1% FBS or DCFBS cell proliferation in SS substantially improved. Ten percent SS plus 10% DCFBS yielded fewer cells on day 7 than conditions with SS plus 1% serum. Apparently, FBS must also contain certain inhibitors of cell growth. When cells were grown in the absence of added estradiol (ED) in DCFBS, cell growth was substantially reduced. Effect of ED is dose-dependent, 0.1 milliM inhibited and 10 nanoM stimulated cell growth. Estrogen (ES) not only stimulated cell growth, it also stimulated the uptake of TDR into cells. Prolactin (PR) by itself, or even in the presence of ES, had no effect upon cell proliferation. The effect of combined treatment with ES and PR on TDR uptake into cells was examined in 10% DCFBS and 10% SS plus 1% DCFBS. ED in absence of PR affected an approx 1.5-fold increase of TDR uptake; with SS, no ED-induced TDR uptake was exhibited. A dichotomous effect of progesterone (PG) upon TDR was observed, low levels of PG had only slight stimulatory effect and had additional stimulation upon ES-induced TDR uptake. PG at 10 uM uniformly inhibited TDR uptake either in the presence or absence of ED. Results indicate that the CAMA-1 cell line is a good alternative model for the investigation of hormonal interaction. (23 Refs)

56. EFFECTS OF ESTROGENS ON CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH CARCINOMA OF THE PROSTATE.

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Urologe [A]; 21(1):34-38 1982

Sixteen patients with advanced carcinoma of the prostate were treated with estrogen therapy (ET) in a prospective study. ET resulted in decreased plasma concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, albumin, antithrombin III, and low density lipoprotein, as well as tissue fibrinolytic activity. ET increased plasma volume and plasma high density lipoprotein levels. ET thus increases the risk of water retention and congestive heart failure. The risk of atherosclerosis may have been reduced. (35 Refs) (In GER)

57. CHARACTERIZATION OF A NEW TYPE OF THYMOMA VARIANT SUPERSENSITIVE TO DEXAMETHASONE.

Mermod JJ, Intriere L, MacLeod CL, Bourgeois S
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J Steroid Biochem; 15:25-34 1981

Some of the properties of dexamethasone supersensitive (Dexss) clones derived from two murine T-cell lines, W7 and T1M1, are described. In the presence of 10(-7) M dexamethasone (Dex), both supersensitive variants are killed faster than their parental line, but the phenotype appears stable. Both D exss variants have the same number of glucocorticoid receptor sites/cell: approx 37,000 Dex binding sites/cell in W7 line and its Dexss variants, and 31,000 sites in the T1M1 line and its Dexss variant. The affinity of these receptors for dexamethasone appears also unchanged in the Dexss variants. No significant difference in the rate of phosphorylation between the parental W7 line and the Dexss variant, and no significant effect of Dex treatment were noticed. Results of lactate and glycogen production studies indicate that no change along the pathway accounts for the supersensitive phenotype of the W7 Dexss variant, and that the pathways are not affected by glucocorticoids in these cells. The supersensitive variant Dexss W7 is more sensitive to cyclic (c)AMP than the parental line; they are approx 10x more sensitive than both T1M1 parental line and the Dexss variant to cAMP. In the presence of 10(-7) M Dex, the addition of calcium has no significant effect on the cell density reached after 24 hr either by the W7 line or its Dexss variant or by T1M1 line and its Dexss variant. General changes in membrane permeability do not account for the supersensitive phenotype of the W7 Dexss variant. (29 Refs)

58. CHARACTERIZATION OF AN EARLY INHIBITORY EFFECT OF GLUCOCORTICOIDS ON STIMULATED ADRENOCORTICOTROPIN AND ENDORPHIN RELEASE FROM A CLONAL STRAIN OF MOUSE PITUITARY CELLS.

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Endocrinology; 110(3):892-900 1982

The ability of glucocorticoid steroid hormones to inhibit release of ACTH and endorphin has been studied in the mouse pituitary tumor cell strain, AtT-20/D16v. Inhibition of release of both peptides was first detectable at 30 min (to 80-90% of control release) and was maximal (30-50% of control) by 3-4 hr of pretreatment with dexamethasone (1 x 10(-6) M). Glucocorticoids did not consistently affect basal hormone release, but they inhibited release stimulated four- to eightfold by hypothalamic extract, phorbol esters, or 8-Br-cAMP but not high K-stimulated release. The inhibitory effect was glucocorticoid specific and dose dependent with ED50S for dexamethasone, corticosterone, and cortisol close to their reported Kds for binding to the cytoplasmic glucocorticoid receptor. Inhibition of release was blocked by cycloheximide (1 x 10(-5) M), suggesting that protein synthesis was required. Experiments were performed to determine the site of action of glucocorticoids. Steroid pretreatment for up to 6 hr had no effect on total intracellular content of ACTH or beta-endorphin, hormone biosynthesis, or intracellular and extracellular hormone degradation. These results show that the inhibitory action of steroids was not due to decreased hormone synthesis, as has been reported after longer periods (24-72 hr) of glucocorticoid treatment. Exper iments with the tumor-promoting phorbol esters (used as model secretagogues) showed the pretreamtent of D16 cells with dexamethasone (1 x 10(-6) M) did not alter the binding of [3H]phorbol dibutyrate to its specific receptor on these cells, indicating that glucocorticoids do not act by interfering with binding of secretagogues to the cells. Furthermore, glucocorticoids did not affect the ED50 for stimulation of ACTH release by phorbol esters, but they reduced the magnitude of maximum response. We conclude that an early action of glucocorticoids on D16 cells is to inhibit the release of ACTH and beta-endorphin by a mechanism that is independent of the synthesis and degradation of the secretory peptides but which involves the synthesis of new protein. (Author abstract) (31 Refs)

59. ORGANIZATION OF PROVIRAL DNA AND PROTEIN COMPOSITION OF HORMONALLY STIMULATED C57BL/10 STRAIN-ASSOCIATED MOUSE MAMMARY TUMOR VIRUS.

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Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):647-659 1981

Two continuous lines, BL-MaTU/A1 and BL-MaTU/S6, were established from C57Bl/10 mammary adenocarcinomas induced by DMBA-prolactin-estradiol treatment. Under in vivo stimulation with dexamethasone, insulin, prolactin, and prostaglandin A1, the cells produce detectable amounts of B-type particles with biochemical properties similar to the GR-MuMTV. Analysis of restriction endonuclease-generated fragments of cellular DNA revealed identical patterns in the integration sites and internal recognition sites of MuMTV proviral equivalents in the tumor cells and normal organs of C57Bl/10 strain mice. The restriction DNA fragments of C57Bl/10-associated MuMTV proviral DNA are closely related to those of the Balb/c-associated MuMTV. These results indicate the endogenous origin of MuMTV produced in the hormonally stimulated cultures of DMBA-prolactin-estradiol-induced C57Bl/10 mammary tumors. (Author abstract) (35 Refs)

60. INCREASED INDUCTION OF SISTER CHROMATID EXCHANGE BY DIETHYLSTILBESTROL IN LYMPHOCYTES FROM PREGNANT AND PREMENOPAUSAL WOMEN.

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Cancer Res; 42(3):893-896 1982

Cultures of whole blood from pregnant women (4 to 6 mo), premenopausal women, postmenopausal women, and normal men were grown in the presence of varying concentrations (1 x 10(-5) M, 2 x 10(-5) M, and 4 x 10(-5) M) of diethylstilbestrol (DES), a synthetic estrogen and known carcinogen, to see if it had sex-related cytogenetic effects. DES induced sister chromatid exchanges in lymphocytes from pregnant and premenopausal women but had only a small effect at the highest concentration (4 x 10(-5) M) in lymphocytes from men and postmenopausal women. At all concentrations, the av number of sister chromatid exchanges was higher in lymphocytes from pregnant women than in those from premenopausal women. In lymphocytes from both a man and a pregnant woman, DES strongly inhibited cell proliferation in vitro. When lymphocytes from a man and a pregnant woman were cocultured in the presence of DES, only the lymphocytes of the woman responded with an increase in sister chromatid exchanges. This indicated that there is no interaction between DES and a factor present in the blood but that DES acts directly on each cell. (Author abstract) (24 Refs)

61. REGULATION BY GLUCOCORTICOIDS OF ARGINASE AND ARGININOSUCCINATE SYNTHETASE IN CULTURED RAT HEPATOMA CELLS.

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J Biol Chem; 257(5):2246-2253 1982

We have examined and characterized the regulation by glucocorticoids of the levels of arginase and argininosuccinate synthetase in two rat hepatoma cell lines (H4-II-E-C3 and MH1C1). Hydrocortisone elevates the activity of both enzymes in a time- and dose-dependent fashion. This effect was blunted markedly by small amounts of ethanol (0.1 to 0.9% [v/v]) and blocked substantially by a high molar excess of the 'anti-inducer' steroid fluoxymesterone. The other 'optimal' inducers dexamethasone and corticosterone were as effective as hydrocortisone in elevating the levels of these enzymes at saturating concentrations. Inhibition of these stimulations by cycloheximide indicated that ongoing cellular protein synthesis was required for both effects, and the admixture of extracts from fully stimulated and basal cells gave no evidence for the existence of direct inhibitors or activators of either enzyme. The results corroborate findings from earlier whole-animal studies and provide evidence for the following conclusions. (i) This stimulation by hydrocortisone of urea-cycle enzymes in the cultured hepatoma cells is mediated by a classical glucocorticoidal mechanism involving initial binding to specific cytoplasmic steroid receptors and the eventual accumulation of new enzyme molecules. (ii) These cell lines thus constitute valid experimental models for use in further detailed studies on the molecular mechanism(s) through which glucocorticoids and intermediary metabolites effect a selective modulation of arginase and argininosuccinate-synthetase gene expression in the differentiated mammalian liver. (Author abstract) (46 Refs)

62. METABOLIC AND ULTRASTRUCTURAL ASPECTS OF THE IN VITRO LYSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS BY GLUCOCORTICOIDS.

Galili U, Leizerowitz R, Moreb J, Gamliel H, Gurfel D, Polliack A
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Cancer Res; 42(4):1433-1440 1982

Human chronic lymphocytic leukemia (CLL) cells like prothymocytes and immunoactivated T-lymphocytes are readily lysed in vitro by pharmacological concentrations of glucocorticoids such as cortisol, whereas peripheral blood lymphocytes and thymocytes are unaffected by the hormone. In this study, metabolic and ultrastructural aspects of the cortisol-induced killing process of CLL cells are recorded. In vitro lysis was found to be temperature dependent and was detected only after 6 to 8 hr incubation with cortisol by means of the trypan blue exclusion test. However, 30 min of incubation with cortisol at either 37 C or 4 C followed by the removal of the hormone was still sufficient to induce the lytic process. Ultrastructural studies demonstrated sequential changes in the cytoplasm, including swelling of mitochondria and cytoplasmic decompartmentalization, followed by loss of surface microvilli with the appearance of 'holes' in the cell membrane, and subsequent condensation of nuclear chromatin. The large holes in the membrane appearing after 6 hr of incubation with the hormone may be the cause for the penetration of the viable stain into the dead cells, as seen by light microscopy. Addition of metabolic inhibitors including actinomycin D, puromycin, and cycloheximide following administration of cortisol resulted in inhibition of the cell lysis. An excess of an antagonist such as cortexolone was found to inhibit the cortisol-induced cytolysis of the CLL cells. It is suggested that the glucocorticoid-induced lysis of human CLL cells is similar to the phenomenon observed in rat or murine lymphocytes and is mediated by interaction of the steroid molecule with the cytoplasmic receptor. The resulting complex appears to activate specific gene(s) the products of which eventually cause cytolysis. (Author abstract) (30 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

63. INCREASED AVAILABILITY OF SERUM ESTROGENS IN BREAST CANCER: A NEW HYPOTHESIS.

Siiteri PK, Hammond GL, Nisker JA, Korenman SG, Topp, Bulbrook RD, Henderson BE, Welsch, Meites, Rosen, Lippman, Sirbascu, Petrakis
Reproductive Endocrinology Center, Univ. California, San Francisco, CA, 94143
Banbury Rep; 8:87-106 1981

Data suggesting a mechanism whereby obesity appears to increase the impact of estrogens on target tissue was studied. Measurements of the percentage of free steroids in serum that closely approximates physiologic conditions indicated that estradiol binding to sex-hormone-binding globulin is of potential physiologic importance. Obesity increases target tissue exposure to estrogen, and chronic stimulation of the breast epithelium over a sufficient period of time, may lead to benign breast disease, and set the stage for cancer in those women who are exposed to an effective dose of virus, irradiation, or carcinogens. (58 Refs)

64. USE OF A GOLD COMPOUND FOR THE TREATMENT OF PEMPHIGUS FOLIACEUS IN A FOAL.

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Dept. Clinical Sciences, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
J Am Vet Med Assoc; 180(4):400-403 1982

A 4-month-old foal was examined because of generalized exfoliative dermatitis, with thick scales, extensive crusting, and oozing of serum. A diagnosis of pemphigus foliaceus was made by histologic and immunopathologic examinations of skin biopsy specimens. The foal was treated with a gold compound, aurothioglucose (1 mg/kg once weekly for 14 weeks). For the initial 5 weeks, high-dose glucocorticoid treatment also was used. The skin disorder resolved entirely after 12 weeks of treatment. (Author abstract) (15 Refs)

65. ENDOMETRIAL CARCINOMA INSENSITIVE TO PROGESTIN AND CYTOTOXIC CHEMOTHERAPY MAY RESPOND TO TAMOXIFEN.

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Acta Obstet Gynecol Scand; 60(6):589-590 1981

Estrogen and progestin receptor-positive endometrial carcinoma, which did not respond with remission to progestin or cytotoxic combination chemotherapy, was sensitive to tamoxifen. This was demonstrated by the complete resolution of pulmonary metastases and pleural effusion, a marked decrease in ESR, and improvement in the general condition of our patient. Although it is very likely that progestin and antiestrogen therapies operate by similar molecular mechanisms, they may be complementary. (Author abstract) (6 Refs)

66. ANTIANDROGENIC THERAPY FOR THE TREATMENT OF EARLY STAGE PROSTATIC CANCER.

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Prostate; (Suppl1):27-34 1981

The antiprostatic action of seven antiandrogens against endogenous and exogenous androgens was measured in immature and mature male rats, respectively. The steroidal agents, in descending order of antiprostatic action against exogenously administered androgen, were cyproterone acetate (CY), chlormadionone acetate (CMA), allylesterol (AE), and oxendrone (TSAA). N-(2-chloromethyl-2-hydroxypropionyl)-3,4,5 trichloroaniline (AA560) and flutamide (FL) were potent antiprostatic agents with exogenous androgens. With endogenous androgens the descending order of effectiveness of the steroids was CY, AE, CMA, TSAA. AA560 and FL were potent in the presence of endogenous androgens. A clinical trial was conducted with 45 patients (stages: A, 4; B, 4; C, 18; D, 19) who received CMA from the outset and 7 patients (C, 2; D, 5) who previously had another therapy. Daily po doses of 100 mg were administered, and changes in plasma levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were determined by radioimmunoassay. Testosterone, LH, and FSH patterns showed a sharp initial decline (4-6 wk) followed by a partial recovery over a 40-mo period; the dose of CMA seemed to be affecting the hypothalamic-pituitary axis function. The trial was expanded to an additional 196 patients who had not been treated previously. Survival rates by stage of disease were 83.3%, A B; 72.6%, C; and 10.6%, D. (6 Refs)

67. CHEMOTHERAPY OF ADVANCED PROSTATIC CANCER WITH PEPLOMYCIN.

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Prostate; (Suppl1):103-110 1981

Thirty-five patients with advanced prostatic carcinoma were administered either peplomycin (PEP: 5-10 mg im, 3x/wk) or estrogen (ES: 30 mg hexestrol daily). The two treatment groups did not differ in tumor reduction rates for previously untreated patients, but for those with relapse after endocrine therapy 3/11 PEP-treated patients exhibited greater than 50% reduction of tumor size vs 0/10 for the ES-treated patients. PEP-treated patients of both previously-untreated and endocrine-relapse groups exhibited greater decreases in serum alkaline phosphatase than did the respective ES-treated patients. For serum acid phosphatase the responses were greater in both types of patients who were treated with ES than in those receiving PEP, but the differences were not statistically significant. PEP was ineffective against bone metastases in both groups of patients; it was effective in both groups against poorly-differentiated cancer. Overall PEP was not more effective in the previously-untreated patients but was superior to ES therapy in the relapsed patients. Adverse effects of PEP were observed in 62.5% of the patients; fever and respiratory disturbances were most common. (21 Refs)

68. THE THERAPEUTIC EFFECT OF CONCURRENT ADMINISTRATION OF 5-FLUOROURACIL AND ALLYLESTRENOL OR HEXESTROL IN SMALL DOSES ON PROSTATIC CARCINOMA.

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Prostate; (Suppl1):111-117 1981

A group of 24 patients (47-87 yr old, av 70 yr) with prostatic carcinoma, including 4 with disease refractory to estrogen therapy, 14 whose disease had been controlled greater than a year, and 6 who were newly diagnosed, were all given 200 mg 5-fluorouracil (5FU) daily. In addition 13 also received 20 mg/day hexestrol (HE) and 50 mg/day allylestrenol (AE). Results were evaluated using a 'vital score' approach, with measurements at 3, 6, and 12 mo during the course of therapy. Both 5FU and AE alone were not as effective as large doses of HE, although they did appear to act additively to suppress prostatic carcinoma. The groups receiving 5FU AE and 5FU HE did not differ from each other in terms of response. For all 24 patients the therapeutic effectiveness was 100% at 3 mo, 77% at 6 mo, and 71% at 12 mo. (7 Refs)

69. MODULATION OF LEUKAEMIA BLAST COLONY GROWTH BY STEROID HORMONES.

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Br J Haematol; 50(2):247-255 1982

The effect of steroid hormones on in vitro colony growth of human myelogenous leukemia cells was examined. Beta-estradiol,testosterone and 5-beta-dihydrotestosterone had little effect on HL60 promyelocytic leukemia cells or blast colony forming cells (CFC) from eight patients with acute non-lymphocytic leukemia (ANLL). These compounds inhibited blast colony growth at very high concentrations (10(-6)-10(-4) M). In contrast, hydrocortisone (HC) had highly variable effects on blast colony growth. HL60 cells were resistant to HC at concentrations up to 10(-4) M but blast CFC showed a wide range of response. Some patients were resistant to HC at all concentrations tested, while others were inhibited by concentrations as low as 10(-8) M. The inhibitory effect of HC was also observed on 3H-TdR incorporation by stimulated peripheral blood blasts. Inhibition by HC was not blocked by progesterone, suggesting this effect was not mediated by specific hormone receptors. These data indicate differences in the response of blast cells in ANLL and normal progenitors to steroid hormones. Cells from patients with ANLL display variable inhibition by HC which is probably not mediated by specific receptors. (Author abstract) (30 Refs)

70. MECHANISMS OF ESTROGEN AND ANTIESTROGEN ACTION IN MAMMARY CANCER.

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Dept. Physiology and Biophysics, Univ. Illinois, Urbana, IL, 61801
J Steroid Biochem; 15:219-229 1981

Estrogen antagonist and estrogen agonist actions of antiestrogens (AE) in ovarian-dependent and autonomous rat mammary tumors (RMT) and in human MCF-7 breast cancer cells were studied. RMT were 7,12-dimethylbenz(a)anthracene (DMBA)-induced in virgin female Sprague-Dawley rats. R3230AC RMT were induced in 40-day-old female Fischer 344 rats. After U23,469 treatment, approx 90% of receptors are found in the nucleus, and the progesterone receptor level is similar to that of the controls and is considerably higher than in RMT regressing due to ovariectomy. AE also influence the level of prolactin binding in DMBA-induced RMT. Administration of U23,469 and two related AE, U11,100A and CI628, beginning at the time of R3230AC tumor transplantation resulted in 2-4 fold depression of tumor growth rate, and the degree of reduction is related to the dose of AE. R3230AC tumor growth is also depressed by estradiol-17 beta while growth is at or slightly above the control rate in ovariectomized hosts. AE treatment increased peroxidase activity (PA) 3-fold, and when AE was administered along with estradiol, mammary tumor PA was only stimulated to the level seen with AE alone. Ovariectomy had no effect on the level of PA in tumors. In vivo studies in the rat utilizing tritium labeled AE revealed that AE are converted to metabolites with increased binding affinity (BA). U23,469 metabolites BA is 50x greater than that of U23,469, while CI628 metabolite binds approx 20x better than the parent compound. Results suggest the existence of differences in chromatin interaction that may underlie the antagonist character of AE. (51 Refs)

71. MEDICAL ADRENALECTOMY IN PATIENTS WITH ADVANCED BREAST CANCER.

Horsley JS, Newsome HH, Brown PW, Neifeld JP, Terz JJ, Lawrence W
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Cancer; 49(6):1145-1149 1982

Medical adrenalectomy, consisting of aminoglutethimide plus either dexamethasone or hydrocortisone, was administered to 53 women with advanced breast cancer. Sixteen (30%) patients had an objective response, 5 patients had stabilization of disease, 26 patients demonstrated progression of disease, 2 patients did not adhere to protocol, and 4 patients had severe toxicity necessitating discontinuation of the drugs. Medical adrenalectomy accurately predicted response to subsequent surgical adrenalectomy in 23 patients. Estrogen receptor (ER) data accurately predicted response (8 of 9 (89%) ER-positive patients responded) or failure (only 2 of 14 (14%) ER-negative patients responded) to medical adrenalectomy. Thirty (of 51 women adhering to protocol) had no toxicity. Therefore, it appears that medical adrenalectomy is safe, usually well tolerated, and can accurately predict response to surgical adrenalectomy. Its use should be limited to ER-positive patients, and it may totally supplant surgical adrenalectomy in the management of advanced breast cancer. (Author abstract) (24 Refs)

72. GYNECOMASTIA IN MEN FOLLOWING ANTINEOPLASTIC THERAPY.

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Wisconsin Clinical Cancer Center, K4/642 Clinical Science Center, 600 Highland Ave., Madison, WI, 53792
Arch Intern Med; 142(3):511-513 1982

Six men had painful gynecomastia develop during or following the administration of cytotoxic chemotherapy. Alternative causes of gynecomastia were not delineated in any patient. Sharp increases in levels of plasma follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were noted in five patients. Plasma testosterone concentrations were within or above the normal range in all five patients in whom they were determined. In three patients, plasma estradiol concentrations were modestly increased. One patient was studied prospectively: painful gynecomastia developed at a time when plasma FSH and LH levels were elevated, serum testosterone was decreasing from supranormal to low-normal concentrations, and plasma estradiol was rising to high levels. Plasma prolactin levels were increased in one of four patients in whom they were measured. The mechanisms leading to gynecomastia following cytotoxic chemotherapy were not defined. Damage to germinal epithelium and Leydig cells as well as changes in the peripheral metabolism of testosterone and estrogen may be important. Gynecomastia may occur following cytotoxic chemotherapy and does not necessarily ,represent recurrent or progressive cancer. (Author abstract) (24 Refs)

73. PERMISSIVE ROLE OF THE PITUITARY IN THE INDUCTION AND GROWTH OF ESTROGEN-DEPENDENT RENAL TUMORS.

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Cancer Res; 42(3):1015-1019 1982

Prolonged administration of estrogen to hamsters by implanted pellets induces not only renal adenocarcinomas but also enlarges pituitaries with hyperplastic and neoplastic changes, especially in the pars intermedia. The pituitaries of the diethylstilbestrol-implanted animals weigh 90 to 150 mg; those of control animals without diethylstilbestrol pellets weigh 7 to 12 mg. Castrated male hamsters were hypophysectomized, implanted with diethylstilbestrol pellets, fed laboratory chow ad libitum, and given 5% glucose in water to drink. New pellets were implanted every 3 mo, and the animals survived for 12 to 15 mo. At autopsy, none of the animals had a tumor. Sixty-two of 65 control castrated males with the same schedule of pellet implantation developed tumors. Hypophysectomized castrated males implanted with diethylstilbestrol pellets were given daily injections of 1 ug each of follicle-stimulating hormone, luteinizing hormone, and prolactin; or with 0.9% NaCl solution. These animals survived for 12 to 15 mo, but none developed kidney tumors. Other castrated males were hypophysectomized and implanted with diethylstilbestrol pellets, and 2 mo later tumor tissues were transplanted under the kidney capsule. Eighty days later, no tumors were evident in the kidneys of these animals. Control castrated males were implanted with diethylstilbestrol pellets, and 2 mo later tumor tissue was transplanted under the kidney capsule. Between 60 and 85 days later, 13 of the 15 controls had developed renal tumors. The concentrations of circulating follicle-stimulating hormone and luteinizing hormone in animals with diethylstilbestrol implants decreased with time and, by 7 mo, were similar to those in hypophysectomized animals. The concentration of prolactin in animals with diethylstilbestrol pellets increased with time and reached twice the value in the control animals without diethylstilbestrol pellets. These studies suggest that some factor secreted by the pituitary may be involved as a promoter or a cocarcinogen in the estrogen induction of kidney tumors. (Author abstract) (19 Refs)

74. PHASE II TRIAL OF TAMOXIFEN IN METASTATIC CARCINOMA OF THE PROSTATE.

Glick JH, Wein A, Padavic K, Negendank W, Harris D, Brodovsky H
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Cancer; 49(7):1367-1372 1982

Fifty-one patients with advanced metastatic carcinoma of the prostate were treated with the antiestrogen tamoxifen. Thirty-eight of these patients were refractory to prior hormonal manipulation with estrogens and/or orchiectomy, and five (13%) achieved an objective response (partial regression or stable disease using the National Prostate Cancer Project criteria). Median survival of the responders was significantly longer than that of the nonresponders (p less than 0.05). An additional 13 patients who had not previously received hormonal manipulation were treated with tamoxifen; one partial response and three disease stabilizations were noted. Response was separately evaluated for 15 patients with objectively measurable lesions using standard Phase II response criteria. Only 1/15 (7%) partial response and 3/15 (20%) disease stabilizations were documented. Subjective benefit in terms of significant pain relief was noted in 17/50 (34%) of patients. Toxicity was mild, but two possible 'tumor flares' were noted. These results do not support the continued investigation of tamoxifen in advanced carcinoma of the prostate. (Author abstract) (22 Refs)

75. CONSIDERATIONS FOR THE USE OF TESTOSTERONE WITH SYSTEMIC CHEMOTHERAPY IN PROSTATIC CANCER.

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(c/o Whitmore) Urology Service, Memorial Hosp., 1275 York Ave., New York, NY, 10021
Cancer; 49(7):1373-1377 1982

Among 52 patients with metastatic adenocarcinoma of the prostate who were treated with exogenous testosterone, 45 (87%) experienced unfavorable subjective and/or objective responses. These unfavorable responses were elicited more frequently and after shorter treatment periods in patients in symptomatic relapse following endocrine therapy than in untreated patients or patients in remission following endocrine therapy. Serious morbidity or mortality, seemingly due to the testosterone administration, occurred in eight cases (15%). It is not known if the action of chemotherapeutic agents will be enhanced by concurrent testosterone therapy, but any such investigation should be undertaken with extreme caution. (Author abstract) (24 Refs)

76. INHIBITION BY 17BETA-ESTRADIOL OF THE GROWTH OF THE RAT PITUITARY TRANSPLANTABLE TUMOR MTF4.

Morel Y, Albaladejo V, Bouvier J, Andre J

(c/o Andre) Laboratoire Biochimie Endocrinienne, UER Lyon-Nord, Hopital Debrousse, 29 Rue Soeur Bouvier, 69322 Lyon Cedex 1, France

Cancer Res; 42(4):1492-1497 1982

The effects of pharmacological doses of estradiol on the growth of the rat pitui tary transplantable tumor MtF4 have been characterized. After sc injection into control rats of a cell suspension prepared from the tumor, in 12 experiments, the av range of days when a new tumor became palpable was between 14.7 -2.3 (SD) and 24.5 -3.3. rats. Daily im injections of 10 ug 17beta-estradiol benzoate or 17beta-estradiol implanted in Silastic tubing partially inhibited the tumor growth as judged by the wt and the time of appearance of the tumor. The same treatments increased the pituitary wt. Both effects were dose dependent above 3 ug 17beta-estradiol benzoate per day and displayed some specificity. 17alpha-Estradiol did not modify the pituitary or the tumor growth significantly; 17beta-hydroxy-3-keto-5alpha-androstane also did not modify the tumor growth. The inhibitory effect of 17beta-estradiol on tumor growth has also been observed in hypophysectomized rats. The tumor cytosol contained 30 to 220 fmol of specific estrogen-binding sites per mg protein which were characterized by: a high affinity (Kd, 0.25 to 0.65 x 10-9M); a sedimentation constant of 6 to 8S; and their hormone specificity. Thus, 17alpha-estradiol, which was inactive in vivo, had an affinity only four-fold lower than 17beta-estradiol. We conclude that pharmacological doses of 17beta-estradiol inhibit in a dose-dependent manner and with some specificity the growth of the MtF4 transplantable pituitary tumor while increasing the growth of pituitary. We suggest this inhibition requires estrogen receptors and is not mediated via the pituitary, but we cannot specify whether this inhibition was direct or not. (31 Refs)

GENERAL REVIEWS ON STEROID HORMONES

77. FEEDBACK CONTROL OF LUTEINIZING HORMONE AND FOLLICLE-STIMULATING HORMONE SECRETION BY TESTOSTERONE AND ESTRADIOL IN MEN: PHYSIOLOGIC AND CLINICAL IMPLICATIONS.

Santen RJ

Dept. Medicine, Div. Endocrinology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033

Clin Biochem; 14(5):243-251 1981

Physiology of the hypothalamic-pituitary-testicular axis (HPTA), clinical application of physiologic principles, clinical disorders of HPTA, diagnosis and treatment of reproductive disorders in men, and new perspectives are reviewed. Differential diagnosis of hypogonatotropic hypogonadism includes diagnosis of hypothalmic and pituitary tumors and functional and anatomic disorders caused by the tumors. (18 Refs)

78. GLUCOCORTICOID RECEPTORS.

Crabtree GR, Smith KA, Munck A
Dartmouth Medical Sch., Hanover, NH
Methods Hematol; 2:252-269 1981

Properties of glucocorticoid receptors (GCR) and general techniques of measuring GCR are presented. Discussion of measurements of GCR in intact cells includes methods, material and equipment requirements, reagents and solutions, assay of nuclear and cytoplasmic GCR, abbreviated single -point assay, and translocation of hormone-receptor complexes. Practical aspects include cell suspensions, incubation conditions, lysis of cells, evaluation of data, estimation of receptor number, and use of stored cells. (44 Refs)

79. RELATIONSHIPS BETWEEN TYPE I AND II ESTRADIOL BINDING SITES AND ESTROGEN INDUCED RESPONSES.

Clark JH, Markaverich BM
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 15:49-54 1981

Cytoplasmic type II estradiol binding sites (EBS), nuclear type II EBS, effects of estradiol and estriol on nuclear type II sites, progesterone and dexamethasone antagonism of type II sites and uterine growth, and differential uterine cell stimulation and the stimulation of nuclear type I and II sites are discussed. Triphenylethylene drugs, such as nafoxidine and clomiphene, stimulating epithelial cells of the uterus while having little effect on stromal or myometrial component, and the discovery of type II sites initiated the examination of the relationship between the two phenomena. The binding of the receptor estrogen complex to nuclear sites is thought to be involved with the stimulation of transcriptional events responsible for cell growth and metabolism. (35 Refs)

80. ADJUVANT CHEMOTHERAPY OF GYNECOLOGICAL TUMORS: THEORETICAL BASES AND TOPICAL STATUS OF CLINICAL EXPERIENCES.

Wetzel V
Landesfrauenklinik, Kaiserallee 10, D-7500 Karlsruhe 1, W. Germany
Therapiewoche; 32(2):136-142,145 1982

Theoretical and clinical aspects of cytostatic chemotherapy (CT) of gynecological tumors are reviewed. In cases of metastatic mammary carcinoma (MC) CT produces a response rate of 62% (complete remission of only 8%) with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) therapy and 72% therapies including adriamycin. Clinical experience indicates that CT is effective against MC only in cases without lymph node metastases (LNM) or with 1-3 LNM. Chances of prolonging recurrence-free time (RFT) or survival time (ST) decrease with increasing numbers of LNM. CT is apparently effective against ovarian carcinoma (OC) in Stages I and II. ST can be prolonged by aggressive CT with ifosfamide or PAC-V therapy. Response to CT depends on differences in cell cycle duration between tumor cells and normal cells. Small tumors generally proliferate faster than larger tumors and have a larger growth fraction. Response to CT thus tends to be more effective against smaller tumors; larger tumors may actually be stimulated by CT. Some proliferative normal tissues, such as bone marrow and gastrointestinal epithelia, may proliferate at faster rates than tumor cells. Phase-nonspecific cytostatic drugs are more effective against tumors than phase-specific drugs when the kinetics of the tumor cells are unknown. Intervals between administrations of CT should be kept as short as possible and doses kept as high as possible to maximize response to CT. Determination of hormone receptor status is an important factor in predicting response. Prediction of response to CT in individual cases is difficult. (58 Refs) (In GER)

81. STEROID RECEPTORS IN EARLY BREAST CANCER: VALUE IN PROGNOSIS.

Nicholson RI, Campbell FC, Blamey RW, Elston CW, George D, Griffiths K

Tenovus Inst. Cancer Res., Cardiff, Wales

J Steroid Biochem; 15:193-199 1981

The relationship of prognosis to estradiol-17 beta receptor (ER)-status of primary breast tumors was studied in 550 patients who presented consecutively to one surgeon (Group A) and in 421 patients dealt with by 15 surgeons (Group B). Systemic treatment of patients after mastectomy was withheld until recurrence of disease. Clinical staging of Group A was by node involvement, and Group B by the international TNM system. Data from both groups indicate no relationship between ER-status and the stage of the disease, nor with tumor size. No advantage is evident by considering the quantity of receptor in the primary tumor since the correlations are not sufficiently strong to allow the prediction of recurrence to be accurately assessed for an individual patient. Group A patients with nodal involvement and ER-positive tumors have, as a group, a more favorable prognosis, approx 70% surviving 3 yr. Node positive ER-positive patients with grade I and II tumors have a good prognosis and do as well as patients without nodal involvement. Tumors with measurable receptor levels were found in 219 patients of Group B. A group of 116 patients without nodal involvement but with ER-negative tumors, despite favorable prognosis, unexpectedly recurred at the same rate as all women with axillary node involvement. Generally the rate of survival was significantly longer in patients with ER-positive tumors. In Group A major local recurrence occurred in 82 patients of whom 42 developed distant metastases and a further 82 had clinical evidence of distant metastases without prior local recurrence. ER-status did not relate to local recurrence, nor to the incidence of 'spot' recurrence. Thirty-one percent of Group A patients with ER-positive primary tumors treated with endocrine therapy responded, while only 5% of the ER-negative tumors were confirmed as responders by external assessment. (30 Refs)

82. BINDING AND BIOLOGICAL RESPONSE OF ANTIESTROGENS IN THE FETAL AND NEWBORN UTERI OF GUINEA-PIG.

Gulino A, Pasqualini JR

(c/o Pasqualini) C.N.R.S. Steroid Hormone Res. Unit, Foundation Hormone Res., 26 Blvd. Brune, 75014 Paris, France

J Steroid Biochem; 15:361-367 1981

Interaction of tamoxifen and several tamoxifen metabolites with macromolecules of fetal uterus were investigated in Hartley albino guinea-pigs and the biological effects elicited by tamoxifen and estradiol were compared in uteri during fetal and neonatal periods of life. Results suggest that biological effects caused by estradiol and tamoxifen could be mediated by the estrogen receptor system and the ability of tamoxifen to induce uterine progesterone receptors appears to be limited as compared to estradiol in fetal uterus suggesting that these two fetal responses are disassociated from each other. (23 Refs)

83. STEROID RECEPTORS IN BREAST CANCER.

Cowan K, Lippman M

Medical Breast Cancer Section, Medicine Branch, NCI, NIH, Building 10, Room 6B02, Bethesda, MD, 20205

Arch Intern Med; 142(2):363-366 1982

Progress in hormone action mechanisms, analysis of estrogen receptors (ER) and progesterone receptors (PR), ER and disease-free interval, and ER and response to cytotoxic chemotherapy (CCT) are reviewed. According to the current hypothesis regarding mechanisms of action, circulating steroid hormones are first taken up by target cells and subsequently bind to specific cytoplasmic receptor molecules. New protein synthesis that occurs in hormone-responsive cells results in changes in the cell phenotype. Reasons for the lack of a perfect correlation between ER status and response to endocrine therapy are the instability of steroid receptors, heterogeneity of malignant cells, existence of numerous endocrine therapies that are ablative and additive, hormone-dependent and independent tumor cells, and the possibility of primarily nuclear location of ER sites and their undetectability in routine assays of cytoplasmic receptors. Patients with tumors that contain both ER and PR have the highest frequency of response (75-80%) to endocrine therapy. Explanations for apparent lack of complete correlation between the presence of PR and response to hormonal therapy are that the biopsy specimens were obtained during the luteal phase of the menstrual cycle and that some postmenopausal patients may actually have concentrations of endogenous estrogen that are insufficient to induce detectable increments of tumor PR activity. ER determination could aid in the selection of a subgroup of women with stage I primary breast cancer who might benefit from early aggressive adjuvant therapy. A definite role of ER status in selection of patients for CCT has not been established. (34 Refs)

84. ORAL CONTRACEPTIVES: VOLUME 5.

Briggs MH, Briggs M

Deakin Univ., Geelong 3217, Australia

Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

Clinical trials, side effects, pharmacology, biochemistry, metabolism, and sociology of oral contraceptives (OC) are reviewed and discussed. Alternatives to the pill, new OC (combined oral products, OC for men), and older OC and therapeutic uses of contraceptive steroids are discussed, including their use in cancer therapy. Mortality and cardiovascular disease, hypertension, thrombosis, amenorrhea, and liver are affected by OC. Malformations and effect on offspring caused by diethylstilbestrol and other contraceptive steroids are reviewed. The role of OC in the genesis of breast, uterine endometrium, cervix, liver, and other neoplasms is discussed. OC may cause neurological, psychological, and other effects. Immunity and infection may be affected by OC. Mode of action, toxicology, contraceptive steroid metabolism, drug interactions, pharmacy, pharmacokinetics, and pharmacodynamics of OC are presented. Biochemistry and metabolism of OC are reviewed focusing on endocrinology (sex hormones, corticosteroids, protein hormones) and vitamins. (1179 Refs)

85. MECHANISM OF HORMONAL DEPENDENCE OF MAMMARY CANCER AND CHOICE OF SYSTEMIC THERAPY.

Gamulin S

Zavod za opcu patolosku fiziologiju, Medicinski Fakultet u Zagrebu, Zagreb, Yugoslavia

Libri Oncol; 10(2/3):159-162 1981

Mechanism of hormonal dependence and choice of systemic therapy in mammary cancer was reviewed. Estrogen and progesterone receptors demonstrate hormonal dependence of some of the mammary cancers. Prognosis as well as efficacy of hormonal therapy in patients with mammary cancer can be indicated. (12 Refs) (In SCR)

86. CLINICAL APPLICATION OF STEROID RECEPTORS IN BREAST CANCER.

Gavrilescu TH

Institutul oncologic, Cluj-Napoca, Romania

Rev Chir [Oncol]; 20(3):179-184 1981

Studies on steroid receptors in breast cancer patients and their therapeutic and prognostic significance are reviewed. Differences were found between patients with estrogen receptor (ER)-positive and ER-negative breast cancers in the free interval before the first recurrence, in survival time from diagnosis, and in the response to hormone therapy and possibly also to chemotherapy. (60 Refs) (In RUM)

87. EXOGENOUS ESTROGENS: A CONTINUING CONTROVERSY.

Malkasian GD

Dept. Obstetrics and Gynecology, Mayo Clinic, 200 First St., SW, Rochester, MN, 55901

Geriatrics; 37(3):79-81,85-86,88 1982

The possible connection between exogenous estrogen (EE) and myocardial infarction (MI) and endometrial (EC) and breast cancer (BC), which are leading causes of death in older women is discussed. In a prospective study, EC patients and matched controls were evaluated for estrone and estradiol; no significant difference in the two groups was noted. Although multiple objections have been raised to current studies of EE and EC, a chronologic survey of the literature appears to yield consistent results with clear clinical implications. Cited data collectively and consistently show the woman who is a long term estrogen user to be at increased risk for EC, at no increased risk for MI, and at no increased risk for BC. Precise indications for the use of EE have to be determined. The potential user has to be evaluated, the risks discussed, and a monitoring program set up which the patient must follow strictly. Evaluation should include a complete history and physical, with precise attention to wt, blood pressure, breast, bone, and vaginal epithelial condition, Papanicolaou smear, and uterine size. The history should take note of parity, tendency to fluid retention, previous cardiac failure, BC or EC, deep thrombophlebitis, and presence or absence of uterus. The estrogen chosen should be the smallest amount that might control the symptoms of menopause, used in a cyclic manner and for a short duration. A follow-up annual physical examination is necessary, plus immediate endometrial sampling on any reported uterine bleeding, or breast biopsy for palpable mass. (26 Refs)

OTHER RELATED STUDIES

88. CALCIUM REGULATION.

Raisz LG
Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Connecticut Health Center, Farmington, CT, 06032

Clin Biochem; 14(5):209-212 1981

Normal calcium regulation depends on the complex interactions of several systems. The specific calcium regulating hormones, parathyroid hormone, calcitriol and calcitonin, affect calcium and phosphorus concentration and supply by acting on bone, kidney and intestine. The changing concentration and supply of ions not only regulate these hormones, but may also influence the function of the target organs, particularly bone, directly. Systemic hormones such as growth hormone and somatomedins, glucocorticoids, sex hormones and thyroid hormone are essential for skeletal growth and development and interact with calcium regulators. Prostaglandins and osteoclast activating factor may be important in local regulation of bone. Disorders of calcium regulation are common, particularly hypercalcemia; however, measurements of parathyroid hormone are not yet ideal and the factors which produce hypercalcemia in malignancy have not been identified. The role of calcium regulating hormones in the pathogenesis and treatment of osteoporosis is controversial. Solution to these problems may be dependent on the identification of additional factors which influence mineral metabolism. (Author abstract) (30 Refs)

89. STUDIES ON THE MECHANISM OF MINERALOCORTICOID-INDUCED HYPERTENSION: EVIDENCE FOR THE PRESENCE OF AN IN-SITU MECHANISM IN THE ARTERIAL WALL FOR A DIRECT ACTION OF MINERALOCORTICOIDS.

Kornel L
Steroid Unit, Dept. Medicine (Endocrinology), Biochemistry, Rush Presbyterian-St. Luke's Medical Center, Chicago, IL, 60612

Clin Biochem; 14(5):282-293 1981

Data from clinical and experimental studies indicate that mechanisms for action of mineralocorticoids, other than renal, must be involved in the overall effect of mineralocorticoids on circ ulation - increased peripheral resistance and hypertension. We have postulated existence of such a mechanism in the arterial wall and have looked for the evidence of its presence. We have found high affinity, specific binders for mineralocorticoids, and glucocorticoids, with characteristics of steroid receptors, in rabbit and lamb arterial homogenate cytosol. Moreover, these binders were found to also possess other fundamental properties of cytoplasmic steroid receptors. The mineralocorticoid with the highest affinity for the arterial mineralocorticoid receptor is 11-desoxycorticosterone (DOC). Cytoplasmic mineralocorticoid receptors are not present in veins. The steroid with the highest affinity for the arterial glucocorticoid receptor is dexamethasone, similarly as in other target tissues to glucocorticoids. Furthermore, we have studied the effect of chronic administration of DOC acetate (DOCA) in intracellular sodium concentration [Nai] and on the rate of passive Na influx into the cells of aorta. Both were found to be significantly higher in DOCA-induced hypertensive rabbits than in normotensive control animals. This indicates that cell-membrane permeability to electrolytes is increased as a result of chronic elevation of circulating levels of DOC, and is in accord with the findings of other investigators in other animal species. We postulate that this effect of DOC is elicited through the receptor-mediated mechanism for action of mineralocorticoids in the arterial wall; and that increased [Nai] in arterial and arteriolar smooth muscles leads to their increased contractility, hyperresponsiveness to vasoconstrictive stimuli, hypertrophy, increased peripheral resistance, and hypertension. (58 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. HISTOLOGICAL AND ENDOCRINOLOGICAL STUDIES ON PROSTATIC CARCINOMA.

Fujii H
Dept. Urology, Yokohama City Univ. Sch. Medicine, Yokohama, Japan
Nippon Hinyokika Gakkai Zasshi; 72(11):1413-1428 1981

Various histologic features of prostatic carcinomas, together with intracellular conversion of testosterone to 5alpha-dihydrotestosterone (DHT), were studied in 22 patients with untreated prostatic cancer, 6 under hormonal therapy for reactivated prostatic cancer, 2 with temporary reactivation of prostatic cancer, 2 with prostatic cancer in remission, and 9 with prostatic hypertrophy. The conversion of testosterone to DHT was used as a biological marker for androgenic activity in the prostatic carcinoma tissues. The rate of conversion was 49.8 +-11.9% for the patients with prostatic hypertrophy, 26.4 +-9.7% for those with untreated cancer, 32.9 +-2.1% for those with cancer in remission, 31.3 +-10.2% for those with temporary reactivation, and 14.7 +-4.3% for those with hormonally treated reactivated cancer. Low grade carcinoma had significantly higher conversion of testosterone to DHT (36.2 +-2.3%) than did high grade carcinoma (24.9 +-4.5%). With respect to histological patterns of the carcinomas, the conversion to DHT was highest (40.0 +-8.2%) in tumors with single gland patterns and was lowest (14.8 +-4.3%) in tumors with medullary or column and cord patterns. Measurement of DHT conversion rates was thought to have clinical value and potential in histological analysis and determination of biological properties of prostatic cancer cells when such measurement was combined with needle biopsy. (29 Refs) (In JPN)

2. RESPONSE TO LUTEINIZING RELEASING HORMONE, THYROTROPHIC RELEASING HORMONE, AND HUMAN CHORIONIC GONADOTROPHIN ADMINISTRATION IN HEALTHY MEN AT DIFFERENT RISKS FOR PROSTATIC CANCER AND IN PROSTATIC CANCER PATIENTS.

Hill P, Wynder EL, Garbaczewski L, Garnes H, Walker AR
American Health Foundation, Valhalla, NY, 10595
Cancer Res; 42(5):2074-2080 1982

A comparative study of the pituitary and testicular response to luteinizing releasing hormone (LHRH), thyrotrophic releasing hormone (TRH), and human chorionic gonadotrophin (HCG) administration was carried out in (a) low-risk young South African black and high-risk North American black men for prostatic cancer and (b) healthy elderly South African men and South African black men with prostatic cancer. A comparable HCG response occurred in young South African and North American black men, while a greater release of prolactin, but a lesser release of luteinizing hormone in response to LHRH:TRH occurred in South African black men. The response to HCG was comparable in elderly and young South African black men, although the prolactin release in response to TRH was greater in elderly men. A more prolonged release of luteinizing hormone was evident in men with prostatic cancer. Higher estradiol and estrone but lower androstenedione levels occurred in men with prostatic cancer. Data suggest that, in the elderly South African black men with prostatic cancer, estrogen metabolism is modified and that either the estrogen level or the higher estrogen:androgen levels modify the pituitary response to LHRH:TRH. A Western diet enhanced the changes in hormone profiles evident in black South African men with prostatic cancer. (Author abstract) (72 Refs)

3. HORMONAL ACTIVITY IN SOME BRENNER'S TUMORS.

Jaluvka V, Kratzsch E
Klinikum Steglitz, Frauenklinik der Freien Universitat Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Gynaekol Rundsch; 22(1):1-22 1982

A hormonally active Brenner's tumor (BT) in a 69-yr-old woman is reported. The patient had been treated for an exulcerative mammary neoplasm of the left breast with metastases in the supra- and infraclavicular and axillary lymph nodes. Treatment consisted of irradiation (tumor dose of 5,000 rad) followed by cytostatic therapy with Proresid, estrogen, and glucocorticoids. Seven mo later a glandular cervical polyp was removed. Histological studies showed a hormonally deregulated endometrium with glandular-cystic hyperplasia and chronic inflammation in the area of epidermized glandular erosion of the cervix. Six mo later heavy bleeding from the uterus developed. Urinary excretion of estrogen was 93.4 ug/24 hr. After another 8 mo hysterectomy with bilateral removal of adnexa was performed. A small BT was found in the left ovary. The patient was treated 2 yr later for progression of mammary carcinoma. Urinary excretion of estrogen was high at this time. Long-term Progynon (PG) depot treatment prevented evaluation of the adrenal cortex role in estrogen formation. Four wk after PG application urinary excretion of estrogen was 564.2 ug/24 hr. The patient responded poorly to therapy and died after development of neurological disturbances resulting from cerebral metastases. Review of literature and present findings indicates that hormonal activity of BT has not been conclusively proven. (106 Refs) (In GER)

4. OESTROGEN PRODUCTION IN ADIPOSE TISSUE FROM NORMAL WOMEN AND WOMEN WITH ENDOMETRIAL CANCER IN VITRO.

Folkerd EJ, Reed MJ, James VH
Dept. Chemical Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
J Steroid Biochem; 16(2):297-302 1982

The conversion of androstenedione (AND) to estrone (ES), and ES to estradiol (ESL) in human adipose tissue obtained from women of various ages and body wt and from those with endometrial cancer was investigated. Subcutaneous adipose tissue was obtained from the abdominal wall of women undergoing gynecological surgery. The conversion of AND to EST in adipose tissue was not correlated with the percentage excess wt of the women. The mean conversion of AND to EST for women 40-50 yr old was 19.6 picog EST/mg protein/3 hr, compared with 3.2 picog EST/mg protein/3 hr in women between 20 and 39 yr. Postmenopausal women had conversion rates less than 11 picog/mg protein/3 hr, indicating that the efficiency of aromatization may decline in later years. The mean conversion of EST to ESL in women 40-50 yr old was 5.1 nanog/mg protein/hr, compared with 1.3 nanog/mg protein/hr for women 20-39 yr old. No increase in rate of conversion of AND to EST in sc adipose tissue was observed in women with endometrial cancer compared with normal women of similar age and wt. In one woman with endometrial cancer, a high rate of conversion of AND to EST (104 picog/mg protein/3 hr) was observed, while the conversion of EST to ESL was lower (1.3 nanog/mg protein/hr), indicating that steroid metabolism is not uniform in adipose tissue throughout the whole body. Thus, adipose tissue can aromatize AND to EST and reduce EST to ESL in vitro. (22 Refs)

5. IN VITRO PREGNENOLONE METABOLISM BY MOUSE ADRENAL GLAND: II - BIOSYNTHESIS OF ANDROGENS.

Edery M, Carreau S, Simon MJ, Drosdowsky MA
Laboratoire de Biochemie, C.H.U. Cote de Nacre, 14040 Caen, France
Steroids; 39(2):191-200 1982

Adrenal gland homogenates from four different strains of mice were incubated with (4-14C)-pregnenolone and a NADPH generating system. The most important androgen synthesized was dehydroepiandrosterone; testosterone and progesterone were synthesized to a lesser extent and the production of androstenedione was very low. The highest synthetic activities were found in the high mammary tumor strain of mice (C3H x RIII) F1; they were increased by ovariectomy, particularly when performed at 2 mo of age. In the other strains, they were lower, specially in the low mammary tumor strain C57BL. However, the 3beta-hydroxysteroid dehydrogenase/delta5,4 isomerase activity was not modified by ovariectomy in the high mammary tumor strain whereas it was increased in the low mammary tumor strains. These results indicate that the androgen synthesis in mouse adrenal depends on factors such as age, sex, endocrine status (ovariectomy) but also on susceptibility to mammary tumor development. (Author abstract) (21 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

6. SIDE-SPECIFIC HORMONE DETERMINATION IN BLOOD FROM THE SPERMATIC VEIN FOR LOCALIZATION OF NON-PALPABLE TESTICULAR TUMORS.

Kopper B, Braedel HU, Biro G, Neisius D, Schwaiger R
Urologische Universitatsklinik, 6650 Homburg/Saar, W. Germany
Therapiewoche; 32(5):542 1982

A case of testicular tumor in a 26-yr-old man is reported. The patient exhibited bilateral gynecomastia with elevated estrogen levels in peripheral blood. Palpation of the testicles produced inconclusive findings. Measurement of estrogen levels in right and left spermatic veins by a catheterization method showed high levels in venous blood from the testicle containing the tumor. Similar results were obtained in two additional cases. All three tumors were benign Leydig-cell tumors. Side-specific hormone determination is indicated as a useful diagnostic aid in cases involving nonpalpable or masked testicular tumors. (no Refs) (In GER)

7. HORMONAL SCREENING IN PATIENTS SUFFERING MALIGNANT MELANOMA. A PRELIMINARY APPROACH.

Langohr M, Robyn C, Legros F, Lejeune FJ
Laboratoire de Physiopathology, Free Univ. Brussels, 2 rue Evers, Brussels, Belgium
Protides Biol Fluid Proc Colloq; 29:567-570 1982

Plasma levels of luteinizing hormone, follicle-stimulating hormone (FSH), prolactin, estrone, estradiol, testosterone (T), dihydroxy-epiandrosterone sulfate, and cortisol were determined in 42 patients with malignant melanoma: 14 men, 35-78 yr old; 28 women (4 premenopausal, 26-42 yr old; 15 postmenopausal, 54-72 yr old; 9 hysterectomized, 50-83 yr old). In the men, all values of T were beyond the lower limit of normal concentration. In postmenopausal and hysterectomized women, FSH levels were elevated. All other hormonal levels were normal. (10 Refs)

8. PRODUCTION OF MONOCLONAL ANTIBODIES TO STEROID HORMONES.

Eshhar Z, Kohen F, Lindner HR
Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel
Protides Biol Fluid Proc Colloq; 29:823-826 1982

Monoclonal antibodies to free (estradiol) and urinary steroid metabolites (pregnanediol-3alpha-glucuronide, estrone-3-glucuronide, estriol-16alpha-glucuronide) were produced by hybridomas between P3-X63-Ag8 variants and spleen cells of mice immunized with bovine serum albumin conjugates of the homologous hapten. The antibodies were found to be useful reagents for the development of highly sensitive radioimmunoassays and chemiluminescence based immunoassays for steroid hormones. (11 Refs)

9. HORMONAL CHANGES IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES.

Pavelic K, Pekic B, Gabrilovac J, Bratic-Mikes V, Boranic M
Dept. Experimental Biology and Medicine, Ruder Boskovik Inst., P.O. Box 1016, Bijenicka c. 54, 41001 Zagreb, Yugoslavia
Biomedicine [Express]; 35(6):181-184 1981

Levels of immunologically reactive insulin (IRI), growth hormone (GH), thyroxine, cortisol and ACTH in sera of patients with various hematological malignancies were determined. IRI and GH levels were increased in 80% of the patients regardless of the type of disease. IRI was more elevated in relapse than in remission. Cytostatic treatment returned IRI serum levels to normal. Thyroxine, ACTH and cortisol in serum were higher in only two percent of the patients with hematological malignancies. (Author abstract) (23 Refs)

10. EVALUATION OF THE 6-HOUR INTEGRATED CONCENTRATION OF CORTISOL AS A DIAGNOSTIC PROCEDURE FOR CUSHING'S SYNDROME.

Zadik Z, De Lacerda L, Kowarski AA
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J Clin Endocrinol Metab; 54(5):1072-1074 1982

The diagnostic value of the 24-hr integrated concentration (IC) test of cortisol (IC-24-F) was found to be superior to the value of both urinary 17OHCS and urinary free cortisol tests. The IC-24-F test is too cumbersome for widespread clinical use. The purpose of the present study was to evaluate the diagnostic value of an abbreviated and practical 6-hr IC of cortisol (IC-6-F) test. The IC of cortisol (IC-F) was measured in 68 normal subjects and 13 patients with surgically proven Cushing's syndrome. A portable nonthrombogenic constant blood withdrawal system was used over a 24-hr period. The IC-F was measured in plasma withdrawn during each 0.5 hr period (IC-1/2-F). The mean of 12 consecutive measurements of IC-1/2-F yielded the IC-6-F. The mean of all the IC-1/2-F collected over a 24-hr period constituted the IC-24-F. The IC-1/2-F of the patients and their IC-6-F from 0800-1400 hr, 1400-2000 hr, and 2000-0200 hr overlapped the corresponding levels in the control subjects. There was no overlap between the IC-

24-F and the IC-6-F (from 2000-0200 hr) of the patients and the control subjects. It was concluded that the diagnostic value of a 6-hr IC-F test conducted during the afternoon and early part of the night is equal to the diagnostic value of the 24-hr IC-F test. (Author abstract) (13 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

11. RELATIONSHIP BETWEEN RECEPTORS FOR MOUSE ERYTHROCYTES AND MEMBRANE IMMUNOGLOBULINS IN NORMAL AND LEUKEMIC HUMAN LYMPHOCYTES.

Stoliar A, Giraudo Conessa LC, Astaldi G
Departamento de Medicina Nuclear e Investigacion Inmunologica,, Instituto de Investigaciones Hematologicas Academia nacional de Medicina, Buenos Aires, Argentina
Medicina (B Aires); 41(Suppl):165-169 1981

Relationship between receptors for mouse RBC (MRBC) and membrane immunoglobulins (mIg) of peripheral lymphocytes in 10 healthy controls (HC: 50-70 yr old) and in 14 patients (similar distribution of sexes and age with the HC) with chronic lymphatic leukemia of B cell type (CLL-B) was studied. All the patients received therapy with corticosteroids and were divided into Group A (6 of the patients with lymphocytes less than 10,000/mm square) and Group B (8 with lymphocytes between 10,000-60.000/mm square). MRBC rosettes for HC were 8% +-2, for Group A were 33.17% +-23.3, and for Group B were 9.12% +- %.2. MRBC rosettes after incubation of lymphocytes with different antibodies were 6% +-3, 8.17% +-6.80, and 2.75% +-2.3, respectively, for anti Ig total. Values for anti IgM and anti IgG were similar to the values for anti Ig total, while anti IgD was 3% +-2, 11.17% +-7.6, and 2.75% +-3.90, respectively. Cells with mIg total were 17.5% +-5, 20.83% +-11.90, and 19.12% +-10.6, respectively; specific mIgM was 7.2% +-3.2, 11.83% +-9.4, and 5.37% +-4.8, respectively; specific mIgD was tested only for Group B and was 3.12% +-5, and specific mIgG was 10% +-4.5, 10.5% +-5.2, and 8.88% +-6.46, respectively. Relationships between the different values were considered and some hypotheses advanced. (23 Refs) (In SPA)

12. HISTOCHEMICAL DETECTION OF OESTROGEN RECEPTORS: A PROGRESS REPORT.

Penney GC, Hawkins RA
Univ. Dept. Clinical Surgery, Royal Infirmary, Edinburgh, Scotland
Br J Cancer; 45(2):237-246 1982

Four albumin conjugates of estradiol, labeled with fluorescein or peroxidase to permit visualization under light or fluorescence microscopy, were synthesized. These were used to examine the feasibility of identifying estrogen binding in frozen section by two published histochemical techniques. In a variety of experimental tissues and human breast cancers, binding of the estrogen conjugates was demonstrable, but it appeared nonspecific (ie, rarely displaceable by competitor) and unrelated to estrogen receptor (RE) status of the tissue as determined biochemically by assay with dextran-coated charcoal. Investigation of the fate of the RE through the various steps of a histochemical assay, demonstrated major losses of RE from unfixed tissue or after tissue fixation. The RE also exhibited a 10-50-fold poorer affinity for the conjugates synthesized than for estradiol-17beta and, at the concentrations of conjugate routinely used in histochemical assays, it seems likely that considerable nonspecific binding takes place. These factors may combine to make it (1) difficult to implement such histochemical assays and (2) unlikely that the RE is being detected. (Author abstract) (21 Refs)

13. EVIDENCE FOR THE ORIGIN OF THE UNOCCUPIED OESTROGEN RECEPTOR IN NUCLEI OF A HUMAN BREAST-CANCER CELL LINE (MCF-7).

Geier A, Haimsohn M, Lunenfeld B
Inst. Endocrinology, Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel
Biochem J; 202(3):687-691 1982

The origin of the unoccupied nuclear estrogen receptor (Rn) was studied. Three working hypotheses were investigated: (a) Rn is a dissociation product of the estrogen occupied nuclear receptor (ERn); (b) ERn is only partially occupied, so that additional binding may occur at 0 C (the temperature at which estradiol saturates unoccupied sites); and that (c) Rn is derived from the penetration of unoccupied cytoplasmic receptor (Rc) into the nucleus. The MCF-7 cell line was used as a model in the present investigation. The amount of unoccupied receptors was measured by saturation with 7.5 nM-[3H]estradiol at 0 C, whereas the occupied receptors were measured by exchange at 30 C. The cells at preconfluency were exposed to a meduim fortified with 10 nM-[3H]estradiol for 1 hr, washed and cultured up to 5 days in fresh growth medium. The distribution of estradiol receptors was determined before exposure and during the following 5 days. After 1h exposure only ERn was found in the nuclear fraction. Thereafter ERn declined continuously so that on day 5 it approached 15% of its value measured 1 hr after exposure. Although after 3 days about 80% of ERn disappeared on Rn appeared, which contradicts hypotheses (a) and (b). On Day 4 Rn and Rc appeared simultaneously. The appearance of Rn and Rc was not prevented by culturing the cells in an estrogen-free medium, supporting hypothesis (c). Exposure of cells to increasing concentration of [3H]estradiol (0.1-10 nM) for 1 hr resulted in a parallel increase in ERn without increasing the amount of unoccupied binding sites, which contradicts hypothesis (b). The present study supports the hypothesis (c), ie, Rc may also penetrate the nucleus without binding to estradiol. (Author abstract) (18 Refs)

14. EFFECTS OF ENDOCRINE THERAPY ON STEROID-RECEPTOR CONTENT OF BREAST CANCER.

Taylor RE, Powles TJ, Humphreys J, Bettelheim R, Dowsett M, Casey AJ, Neville AM, Coombes RC
(c/o Coombes) Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 45(1):80-85 1982

In order to determine the mechanisms of relapse following response to endocrine therapy, we have measured the estrogen receptor (RE) content of biopsies of breast cancer in patients receiving various types of endocrine treatment. RE content fell in responding (means of 260.2 to 12 fmol/mg protein) and in nonresponding (means of 155.1 to 31.8 fmol/mg protein) patients who had measurable receptor at the start of treatment. Some of these patients, and a further group of responders to endocrine therapy, were monitored until relapse. Tumor biopsies at the time of relapse showed that 10/14 tumor samples contained significant RE (mean of 86.7 fmol/mg protein; range less than 10-271 fmol/mg protein) after successful endocrine therapy. No relationship could be found between RE content and plasma gonadotrophin or steroid-hormone concentration, but the fall in RE content correlated with reduced numbers of tumor cells in the biopsy. These results indicate that relapse following successful endocrine therapy in breast cancer does not appear to be due to the emergence of RE-negative tumor cells. The fall in RE content during response to endocrine therapy may be due to reduced tumor-cell content of the biopsy. (Author abstract) (19 Refs)

15. TAMOXIFEN ANTIESTROGENS. A COMPARISON OF THE ACTIVITY, PHARMACOKINETICS, AND METABOLIC ACTIVATION OF THE CIS AND TRANS ISOMERS OF TAMOXIFEN.

Robertson DW, Katzenellenbogen JA, Long DJ, Rorke EA, Katzenellenbogen BS
(c/o Katzenellenbogen, J.A.) Dept. Chemistry, Univ. Illinois, 461 Roger Adams Lab., 1209 W. California St., Box 37, Urbana, IL, 61801
J Steroid Biochem; 16(1):1-13 1982

Interaction of tritium-labeled cis and trans isomers of tamoxifen with target tissues was studied, and their pharmacokinetics and metabolism were compared. Observations in immature female Holtzman rats confirmed that the cis isomer is a full estrogen agonist in terms of uterine weight gain but that the trans isomer is both a partial agonist and an antagonist. Both isomers were weak stimulators of uterine peroxidase, but they differed in their ability to antagonize estrogen-stimulated uterine peroxidase: only trans-tamoxifen achieved significant antagonism. After rats were given 5-ug doses of 3H-trans-tamoxifen, polar metabolites accumulated in the uterine nucleus. After administration of the cis isomer, no accumulation of the corresponding metabolites occurred; instead, a small amount of metabolite with polarity between that of cis-tamoxifen and trans-hydroxytamoxifen appeared. Results of in vitro incubations with rat liver microsomes indicated that N-demthylation and hydroxylation of both isomers took place. Hydroxylation produced compounds with substantially increased affinity for the receptor, whereas N-demethylation had only a slight, if any, effect on the inhibitor. Results indicated that significant differences exist in the pattern of metabolites of cis and trans tamoxifen in the uterus; these differences apparently result from differences in affinity of cis and trans isomers of certain metabolites for the estrogen receptor. (29 Refs)

16. VARIANT T47D HUMAN BREAST CANCER CELLS WITH HIGH PROGESTERONE-RECEPTOR LEVELS DESPITE ESTROGEN AND ANTIESTROGEN RESISTANCE.

Horwitz KB, Mockus MB, Lessey BA
Dept. Medicine, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Cell; 28(3):633-642 1982

In target tissues for estrogen, including breast cancer cells, the synthesis of progesterone receptors (PRs) is controlled by estradiol acting through estrogen receptors (ERs). We describe studies with T47D human breast cancer cells, whose PRs are not regulated by estradiol, though present in extraordinary amounts (300,000 sites per cell). These cells have no ERs sedimenting at 8S on sucrose density gradients, and no unfilled cytoplasmic or nuclear ERs; some apparently hormone-filled nuclear sites, with KD approx or equal to 0.7 nM, can be demonstrated by exchange. The nuclear ER sites are not processed after estradiol treatment. Nafoxidine, however, doubles nuclear estrogen binding in 6 hr, in a cycloheximide-insensitive step that may represent a reversal of processing. T47D cells are profoundly resistant to estrogens and antiestrogens; estradiol does not stimulate PRs, and nafoxidine concentrations that are cytotoxic to ER-positive cells have no effect on cell growth or on PR levels. Yet the PRs are normal by several criteria, and they can be stoichiometrically translocated to, and extracted from, nuclei in the first 3 min after progesterone addition. If progesterone treatment exceeds 10 min, rapid nuclear turnover prevents quantitative PR recovery. Cytoplasmic PRs are replenished in 10 to 24 hr, and this cycloheximide-sensitive step is also estrogen- and nafoxidine-resistant. However, despite their insensitivity to estradiol or antiestrogen, PRs are not constitutively synthesized; 5-bromodeoxyuridine and sodium butyrate can selectively inhibit PR production. Thus, since PRs retain some characteristics of inducible proteins, the persistent nucelar estrogen-binding sites may be stimulating PRs continuously, even in the absence of exogenous estradiol. (Author abstract) (45 Refs)

17. ACUTE THERAPY WITH MEGESTROL ACETATE DECREASES NUCLEAR AND CYTOSOL ANDROGEN RECEPTORS IN HUMAN BPH TISSUE.

Geller J, Albert J, Geller S

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Prostate; 3(1):11-15 1982

Acute effects of megestrol acetate (Megace) on cytosol and nuclear androgen receptor concentrations in benign prostatic hypertrophy in five patients were examined. Patients received Megace (120-160 mg/day) for 1-3 days (1 patient) or 10-11 days. The last dose was given the night before transurethral resection of the prostate. Tissues were homogenized and separated into cytosol and crude nuclear fractions. Cytosol and salt extractable nuclear fractions were subjected to saturation analysis with 3H-R1881 over the range of 0.5-10 nanomoles in exchange reactions for 20 hr at 15 C. Significant decreases were noted in cytosol receptor concentration compared with six untreated controls (8.68 +-3.2 vs 32.7 +-7.6 femtomoles 3H-R1881 bound/mg protein), in nuclear receptor concentration (43.8 +-18 vs 317 +-43 femtomoles 3H-R1881 bound/mg DNA), and in serum testosterone (1.01 +-0.25 vs 3.65 +-0.60 nanog testosterone/ml serum). These effects of Megace on receptor concentration are compared with those reported following castration in animals or following high-dose estrogen therapy in humans. The mechanism of action of Megace in decreasing the receptor concentrations in cytosol and nucleus is unclear. (16 Refs)

18. ORAL CONTRACEPTION IN PATIENTS WITH HYPERPROLACTINAEMIA.

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Dept. Endocrinology, Saint Bartholomew's Hosp., London EC1A 7BE, England

Br Med J; 284(6319):868 1982

Estrogen-containing contraceptives are usually contraindicated in hyperprolactinemia, since prolactin-secreting pituitary tumors have estrogen receptors and may rapidly enlarge with estrogen treatment. Whether medical control of hyperprolactinemia could be maintained after oral contraceptive treatment was assessed in 10 women (23-36 yr old). Minilyn (ethinylestradiol 50 ug, lynestrenol 2.5 mg) was well tolerated in the patients, provided that serum prolactin concentrations were first restored to normal with bromocriptine and bromocriptine was continued throughout contraceptive use. (4 Refs)

19. DEXAMETHASONE SYNERGISTICALLY INDUCES CHEMOTACTIC PEPTIDE RECEPTOR EXPRESSION IN HL-60 CELLS.

Skubitz KM, Zhen YS, August JT

Dept. Medicine, Johns Hopkins Univ. Sch. Medicine, 725 North Wolfe St., Baltimore, MD, 21205

Blood; 59(3):586-593 1982

We have examined the effect of physiologic concentrations of dexamethasone on the induction of differentiation of the human promyelocytic leukemia cells (HL-60) and the activity of surface receptors for the f-met-leu-phe chemotactic peptide. Dexamethasone at a concentration of 500 nM was markedly synergistic with dimethylformamide and dimethylsulfoxide, but not with trans-retinoic acid, in inducing f-met-leu-phe binding by HL-60 cells. The increase in peptide binding was due to an increase in the activity of peptide receptors rather than an increase in receptor affinity. The effect of dexamethasone was relatively specific for peptide binding as there was little effect when HL-60 differentiation was assessed by cell morphology or the ability of the cells to reduce nitroblue tetrazolium. Dexamethasone alone had no reproducible effect on HL-60 differentiation as assessed by the three criteria tested. The dexamethasone concentration required for half maximal synergism correlated with the known binding constant of the hormone for steroid receptors in HL-60 cells but the effect of dexamethasone was not blocked with the steroid blocking agents 17 alpha methyltestosterone or progesterone. (Author abstract) (42 Refs)

20. RECEPTOR-DEPENDENT ANTIPROLIFERATIVE EFFECTS OF CORTICOSTEROIDS IN RADIATION-INDUCED FIBROSARCOMAS AND IMPLICATIONS FOR SEQUENTIAL THERAPY.

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Cancer Res; 42(5):1686-1691 1982

Competitive binding studies with [3H]dexamethasone and Scatchard analysis demonstrated a single class of high-affinity, low-capacity glucocorticoid receptor sites in 105,000 x g cytosols from radiation-induced fibrosarcomas. In vivo, both dexamethasone (DEX) and methylprednisolone treatments resulted in dose-dependent inhibition of tumor growth and cell proliferation. Changes in the sensitivity of the clonogenic cell population to 3 mM hydroxyurea were used to assess changes in the clonogenic cell proliferation during and after treatments with DEX or methylprednisolone. Neither methylprednisolone nor DEX given every 12 hr for three doses resulted in significant cell kill in the clonogenic fraction. However, changes in the hydroxyurea sensitivity of the clonogenic population after cessation of DEX treatments indicated G1 cell cycle progression delay with transient enrichment of S-phase clonogenic cells 24 to 48 hr after cessation of DEX treatments. The duration of the DEX-induced progression delay and the timing of maximal S-phase cellularity after DEX was directly correlated with the level of glucocorticoid receptors in the treated tumors. Using regrowth delay to assess the efficacy of kinetically directed sequential chemotherapy, the effectiveness of vincristine, given after DEX, was highly sequence dependent, with the most effective treatment interval being coincident with maximal S-phase clonogenic fraction. Other studies indicated that the effectiveness of cyclophosphamide could also be increased by time sequencing after DEX. (Author abstract) (46 Refs)

21. HETEROGENEITY OF BINDING SITES FOR TAMOXIFEN AND TAMOXIFEN DERIVATIVES IN ESTROGEN TARGET AND NONTARGET FETAL ORGANS OF GUINEA PIG.

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Cancer Res; 42(5):1913-1921 1982

This paper shows that the antiestrogen tamoxifen and different tamoxifen derivatives bind to two distinct cytoplasmic binding sites in the fetal uterus of guinea pig. The first one (Site A) corresponds to the estrogen receptor and binds tamoxifen with a dissociation constant (Kd) of 1.8 +-0.4 nM. The binding ability of Site A appears to be thermolabile, being destroyed by heating at 37 C. The hydroxylated derivatives of tamoxifen (Metabolites B and D) have a higher affinity for Site A as compared to tamoxifen. The second binding site for tamoxifen (Site B) appears to be specific for the triphenylethylene class of antiestrogens the hydroxylation of tamoxifen decreasing the affinity for Site B. In contrast, natural and synthetic estrogens as well as cortisol, testosterone, and progesterone do not compete for Site B. Site B shows a higher affinity for tamoxifen as compared to Site A and a higher stability of the comples at both 4 and 26 C. The binding ability of Site B appears to be resistant to heating at 37 C. Both Sites A and B are destroyed by proteolytic treatment and are precipitated by 36% saturated ammonium sulfate. The tamoxifen:Site A complex translocates into the uterine nuclei in a 'cell free' system by a temperature-dependent process, but the tamoxifen:Site B complex does not. Nevertheless, a site with a Kd similar to cytoplasmic Site B is spontaneously present in untreated fetal uterine nuclei. In other fetal organs which contain no estrogen receptor or very low levels, the concentration of Site B is found to be significantly lower than in the fetal uterus. Furthermore, progressively lower levels of Site B are found in neonatal, immature, and mature uteri which contain also decreasing amounts of estrogen receptors. It is concluded that, besides binding to the estrogen receptor, the triphenylethylene antiestrogens bind to a specific site distinct from the estrogen receptor, that appears to be localized mainly in estrogen target cells. (43 Refs)

22. ESTRONE RECEPTOR FORMATION DURING THE PROCESSING OF ESTRADIOL-RECEPTOR COMPLEX IN MCF-7 CELLS.

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Cancer Res; 42(5):1967-1974 1982

Human breast cancer cells (MCF-7) contain separate estrogen receptors specific for either 17-beta-estradiol or estrone. Utilizing optimum conditions for the protamine sulfate assay, it has been possible to demonstrate both receptors in the 0.6 M KCl extract of nuclei and in the cytosol. Similarly, in the exchange assay, high-affinity low-capacity binding sites for 17beta-estradiol and estrone have been found in the salt-extracted nuclear residue. Dissociation constants and binding capacities were demonstrated for either receptor in the absence of the other or, when both receptors were present, a saturating amount of the other estrogen was added to the assay mixture. Specificity was demonstrated by the inability of estrone to compete with 17beta-[2,4,6,7-3H]estradiol for the 17beta-estradiol receptor at molar excesses less than 10-fold. Likewise, there was no inhibition of [6,7-3H]estrone binding to its receptor by molar excesses of 17beta-estradiol below 100-fold. Other steroid hormones were very weak competitors of [6,7-3H]estrone. The quantitative relationships of these two estrogen receptors were shown to fluctuate in the various cellular compartments following incubation of MCF-7 cells with 10(-8) M 17beta-estradiol. This level of 17beta-estradiol elicited the translocation of all detectable cytosolic E2R to the nucleus, where the salt-resistant 17beta-estradiol disappeared and 40% of the extractable 17beta-estradiol-binding capacity was lost. Simultaneously, the E1R which remained in the nuclear residue appeared in the nuclear extract, and ultimately this receptor accumulated in the cytosol. The estrone-binding capacity which appeared following the processing of E2R nearly equalled the loss of 17beta-estradiol binding sites per cell. Concentrations of 17beta-estradiol which elicited the greatest processing of E2R in these incubations brought about the appearance of max levels of E1R in MCF-7 cells. Processing would appear to involve the formation of estrone receptor (E1R) in the salt-resistant nuclear compartment followed by the accumulation of E1R in the cytosol. (40 Refs)

23. GLUCOCORTICOIDS DOWN-REGULATE SOMATOSTATIN RECEPTORS ON PITUITARY CELLS IN CULTURE.

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Endocrinology; 110(4):1147-1154 1982

Treatment of GH4C1 cells, a clonal strain of rat pituitary tumor cells which synthesize and secrete PRL and GH, with 5 x 10(-6) M cortisol caused a time-dependent decrease in [125I-Tyr1]SRIF-specific binding. Receptor affinity was the same in control and cortisol-pretreated cells, but the number of SRIF-binding sites decreased from 21,900 to 15,200 receptors/cell. Pretreatment of cells with 5 x 10(-7) M dexamethasone (1,4-pregnadien-9-fluoro-16alpha-methyl 11beta,17alpha,21-triol-3,20-dione) for 43 hr caused the same maximal decrease in [125I-Tyr1] somatostatin (SRIF)-specific binding as 5 x 10(-6) M cortisol; however, dexamethasone was 10x more potent than cortisol. Pretreatment of GH4C1 cells for 43 hr with 5 x 10(-6) M 17beta-estradiol, 17alpha-methyltestosterone, testosterone, or progesterone had no effect on [125I-Tyr1]SRIF-specific binding, indicating that this effect was glucocorticoid specific. Treatment of GH4C1 cells with both dexamethasone and cycloheximide caused the same decrease in [125I-Tyr1]SRIF-specific binding as did either agent alone. In contrast, the down-modulation of SRIF receptors by chronic TRH treatment was previously shown to be additive with cycloheximide. However, maximal concentrations of TRH and cortisol added together had no greater effect on SRIF receptors than TRH alone. Therefore, even though the effects of TRH and cortisol are differentially sensitive to cycloheximide, the pathways by which they down-regulate SRIF receptors probably overlap at a common rate-limiting step. In conclusion, the receptors for TRH and SRIF are modulated in opposite directions on GH4C1 cells by chronic glucocorticoid treatment. Since these two hypothalamic peptides have opposing effects on hormone release, such receptor modulation may play an important role in regulating pituitary responsiveness to these hypothalamic regulatory factors. (45 Refs)

24. EFFECT OF ANTIBODIES TO ESTROGEN RECEPTOR ON THE BINDING OF 3H-LABELED ANTIESTROGENS AND ANDROSTANEDIOL IN THE UTERUS.

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Endocrinology; 110(4):1355-1361 1982

We report here the effects of antibodies to estrogen receptor (ER) on the binding of tritiated 5alpha-androstane-3beta-17beta-diol and antiestrogens to receptor in calf uterine cytosol. The antibodies, prepared from a rabbit immunized with purified estradiol-receptor complex from calf uterine nuclei, were found to decrease the affinity, but not the number of binding sites, of ER for 5alpha-androstanediol and tamoxifen [alpha-(4beta-N-dimethylaminoethoxy)phenyl-alpha'-ethyl trans-stilbene]. This appeared to be due to the decrease in the association rate of the ligands, while the dissociation rate was not modified. The ER antibodies did not affect the binding of ER to estradiol or to the monohydroxylated metabolite of tamoxifen, nor did they affect the interaction of androgens with the androgen receptor. The formation of a ternary complex among [3H]hydroxytamoxifen [3H-labeled alpha-(4beta-N-dimethylaminoethyoxy)phenyl-4-hydroxy alpha'-ethyl-trans-stilbene], the ER, and the antibodies was demonstrated by sucrose gradient ultracentrifugation. For [3H]tamoxifen and [3H]5alpha-androstanediol, ternary complexes were also formed with ER bound to monoclonal antibodies linked to Sepharose. These results confirm that ER directly binds androstanediol, tamoxifen, and hydroxytamoxifen. The lower affinity of ligands for ER in the presence of antibodies was only observed for the low affinity ligands and did not appear to be correlated to their antiestrogenic activities. (Author abstract) (25 Refs)

25. EQUINE CUSHING'S DISEASE: PLASMA IMMUNOREACTIVE PROOPIOLIPOMELANOCORTIN PEPTIDE AND CORTISOL LEVELS BASALLY AND IN RESPONSE TO DIAGNOSTIC TESTS.

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Endocrinology; 110(4):1430-1441 1982

Equine Cushing's disease is almost invariably caused by ACTH hypersecretion by adenomas of pars intermedia (PI). PI proopiolipomelanocortin (proOLMC) peptides, such as alphaMSH, betaMSH, corticotropin-like intermediate lobe peptide (CLIP), and beta-endorphin (betaEND), are also secreted. In two horses with Cushing's disease, basal plasma immunoreactive ACTH was elevated about the same as in human Cushing's disease, but alphaMSH, betaMSH, CLIP, and betaEND were disproportionately increased. In the mare with more severe disease, neither low nor high dose dexamethasone suppressed hormone levels; in the less affected mare, high dose dexamethasone suppressed peptide levels only modestly, and cortisol never fell below normal. Both mares had glucose intolerance. Insulin did not lower blood glucose in the mare with severe Cushing's disease and diabetes mellitus; in the other, there was little response of peptides or cortisol, although blood glucose fell to 34 mg/dl. The adrenal cortices of both animals responded to exogenous ACTH. The less affected mare was studied further. The results suggest that proOLMC peptide secretion by a PI adenoma causing equine Cushing's disease is under similar control as normal PI in other species. Glucocorticoids, which suppress pars distalis (PD) but not PI secretion, and vasopressin and hypoglycemia, which stimulate PD but not PI secretion, had little or no effect on PI tumor proOLMC secretion; in contrast, dopamine, which inhibits PI but not PD proOLMC peptide secretion, also inhibited PI tumor secretion and thereby provides a potential rationale for treating Cushing's disease in horses. (55 Refs)

26. STEROID HORMONE RECEPTORS AND THE GROWTH OF UTERINE MYOMA.

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Dept. Obstetrics and Gynecology, N. A. Semashko Medical Stomatological Inst., Moscow, USSR
Akush Ginekol (Mosk); (2):46-49 1982

Relationship between the concentration of steroid hormone receptors and the type of tumor growth was studied in 57 women (28-52 yr old) with uterine myoma. All patients were subjected to surgery: 41 underwent supravaginal amputation of the uterus, 11 underwent extirpation of the uterus, and 5 underwent conservative myomectomy. Indications for surgery included rapid growth of myoma, submucous localization of the myoma nodules, and uterine hemorrhage. Morphological examination of surgery specimens showed stable size of the myoma in 19 patients (Group 1), marked proliferation of smooth muscles or true growth of myoma in 28 (Group 2), and secondary changes associated with edema or dystrophy of myoma nodules in 10 (Group 3). Regardless of the type of myoma growth, concentration of estradiol receptors in the myoma nodule was almost 2x greater than that in the myometrium. Relationship between the concentration of progesterone receptors (PR) in the myoma tissue and in the myometrium depended upon the type of tumor growth: PR concentration in myoma tissue was similar to that in the myometrium in Group 1, exceeded that in the myometrium in Group 2, and was lower than that in the myometrium in Group 3. (10 Refs) (In RUS)

27. HORMONAL THERAPY OF THE ADVANCED BREAST CANCER.

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Arch Geschwulstforsch; 52(3):231-240 1982

Results obtained with hormonal therapy in patients with mammary carcinoma were reviewed. Indications for hormonal therapy by itself or as adjuvant therapy were discussed. Values of estrogen receptors can predict sensitivity to hormonal therapy in 75% of the patients. Prognosis cannot be indicated from presently available methods. (4 Refs) (In GER)

28. STEROID HORMONE RECEPTORS IN MAMMARY CARCINOMA.

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Dtsch Med Wochenschr; 107(8):313-315 1982

Determination of steroid hormone receptors (HR) is of significant prognostic value in cases of mammary carcinoma. Patients with tumors bearing HR respond better to hormonal and cytotoxic therapy than patients with HR-negative tumors. Presence of estrogen receptors is related to age and menopausal status. Presence of progesterone receptors is independent of age and menopausal status. HR status provides useful information about lymph node status, recurrence-free interval, and survival time. (21 Refs) (In GER)

29. STEROID HORMONE RECEPTORS IN HUMAN MELANOMA.

Grill HJ, Benes P, Manz B, Schramm P, Morsches B, Korting GW, Pollow K
Abteilung fur Experimentelle Endocrinologie, Johannes Gutenberg Universitat, Langenbeckstr. 1, D-6500 Mainz, W. Germany
Arch Dermatol Res; 272(1/2):97-101 1982

Results of estrogen (ER), progesterone (PgR), and glucocorticoid receptor (GlucR) determinations in 15 human melanoma are reported. The arithmetic mean of ER was 19.9 femtomoles (fmol)/mg cytosol protein, of PgR was 78.5 fmol/mg protein, and of GlucR was 19.2 fmol/mg protein. Taking the 20 fmol/mg protein as a cutoff value for human mammary tumors, 3 of 15 (20%) ER-, 8 of 15 (53%) PgR-, and 6 of 15 (40%) GlucR-positive melanomas were found. The generally better prognosis of female tumor patients, as detected by statistical analyses, may have its origin in higher estrogen and/or gestagen production. (17 Refs)

30. CORRELATION OF PROSTATIC NUCLEAR ANDROGEN RECEPTOR CONTENT WITH DURATION OF RESPONSE AND SURVIVAL FOLLOWING HORMONAL THERAPY IN ADVANCED PROSTATIC CANCER.

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Dept. Urology, Royal Victoria Hosp., 687 Pine Ave. West, Montreal, Quebec, H3A 1A1, Canada
J Urol; 127(3):466-471 1982

To assess whether pretreatment prostatic androgen receptor measurements would be of value in predicting the response to hormonal therapy in patients with prostatic cancer 23 men with metastatic carcinoma of the prostate underwent prostatic biopsy before treatment. Cytosolic and nuclear prostatic androgen receptor contents were measured by a single saturating dose, dextran-charcoal assay. All patients had measurable levels of androgen receptor in prostatic tissue and all demonstrated objective evidence of improvement following hormonal therapy. Thus, if androgen receptor measurements are to be useful in predicting prognosis correlations between quantitative levels of receptor and quantitative aspects of response must be established. In our study response was quantitated by measuring the duration of response and survival following hormonal treatment. The strong correlation between duration of response and survival (p less than 0.01) demonstrated herein suggests that survival in these patients is related directly to the duration of time patients respond to hormonal therapy. Neither total cellular nor cytosolic androgen receptor content correlated with response. However, nuclear androgen receptor content correlated with the duration of response and survival following hormonal treatment (p less than 0.05). Furthermore, in patients with nuclear receptor levels less than 110 fmol per mg deoxyribonucleic acid the duration of response (7.1 plus or minus 3.8 mo) and survival (14.4 plus or minus 5.9 mo) was significantly shorter than in patients with higher levels of nuclear receptor (17.3 plus or minus 10.4 and 24.7 plus or minus 8.8 mo, respectively (p less than 0.05)). These findings, which are the first report of a correlation between nuclear androgen receptor content and hormonal responsiveness, suggest that measurements of nuclear receptor may aid in identifying those patients unlikely to obtain prolonged response from hormonal therapy. (Author abstract) (25 Refs)

31. ADJUVANT TAMOXIFEN THERAPY FOR EARLY BREAST CANCER: AN EXPERIMENTAL STUDY WITH REFERENCE TO OESTROGEN AND PROGESTERONE RECEPTORS.

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Br J Surg; 69(3):121-125 1982

There is very little known about the subsequent behavior of breast cancer following adjuvant endocrine therapy or the effect of this therapy on the estrogen and progesterone receptor content of recurrent disease. Mammary tumors were induced in Sprague-Dawley rats using N-nitrosomethylurea. In two experiments animals were treated with tamoxifen at different doses prior to the appearance of tumors. Tamoxifen prolonged the induction time and reduced the total number of tumors. Subsequent treatment of established tumors exposed to tamoxifen in the induction period demonstrated a reduced response to further tamoxifen therapy. There was no difference in the estrogen receptor content of the tumors previously exposed to tamoxifen, but there was a significant reduction in the progesterone receptor content. The results suggest that: (a) patients treated with adjuvant tamoxifen therapy will show a delay in the appearance of recurrent disease with a reduced response to further tamoxifen therapy; (b) the model may provide an in vivo method to examine the relationships between estrogen and progesterone receptors and response to endocrine therapy. (Author abstract) (34 Refs)

32. TOWARDS A NEW MODEL FOR THE MECHANISM OF ACTION OF STEROIDS.

Martin PM, Sheridan PJ

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J Steroid Biochem; 16(2):215-229 1982

Localization of estradiol receptor (ER) in uteri from ovariectomized and/or ovariectomized-adrenalectomized Sprague-Dawley rats and several ER+ cell lines was investigated by autoradiography and biochemical procedures. Cells were incubated with 3H-estradiol or 3H-R2858 (methoxy-17-ethinylestradiol) for 5 min to 2 hr at different concentrations of ligands (0.1-10 nanoM) at 4 C. Autoradiography demonstrated a specific nuclear localization of 3H-estradiol after 5 min incubation at 0-4 C. A nuclear uptake and retention of 3H-estradiol at 0-4 C was also demonstrated in some human breast cancer lines and in a clone of estrogen-sensitive rat embryonic pituitary cells in culture. The ratio of specific binding of radioactivity in the nucleus to that in cytoplasm decreased as the concentration of ligand increased. When the cells were processed using biochemical procedures, all binding activity appeared in the cytosolic fraction. Free receptor was demonstrated in the crude nuclear preparations when concentrated preparations of homogenized uteri and several nuclear preparations from cell lines were made. These findings suggest that unbound receptors for estrogen exist in nuclei of the smooth muscle cells of myometrium as well as in nuclei of some of the cell lines tested. A new model for the distribution of ER is proposed in which unbound receptors are in equilibrium, partitioned between nucleus and cytoplasm according to the free water content of these intracellular compartments. (40 Refs)

33. ISOELECTRIC FOCUSING OF OESTRADIOL RECEPTOR PROTEIN FROM HUMAN MAMMARY CARCINOMA - A COMPARISON WITH DEXTRAN COATED CHARCOAL ASSAY.

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J Steroid Biochem; 16(2):239-244 1982

Isoelectric focusing (IEF) of receptor protein in polyacrylamide gel and dextran-coated charcoal (DCC) receptor assays were compared for ability to detect specific estradiol-17beta receptor protein in breast tumor tissue. When IEF was performed on 29 selected cytosols without partial trypsin digestion, 83% of the findings correlated with results obtained with DCC. When trypsin digestion was included in 32 cytosols, 97% agreement on the receptor status was achieved. Quantitative analysis of the positive results demonstrated that those obtained by IEF gave significantly lower values than DCC analysis: the correlation coefficient was 0.88. When 40 freeze-dried samples weighing between 4-55 mg were analyzed by IEF and the results compared with those obtained with DCC, 87% agreement was achieved. With Tru-Cut biopsy samples taken immediately before mastectomy (2-34 mg), qualitative agreement was 88% between IEF and DCC, with no significant difference between the quantitative results of the two methods. A correlation coefficient of 0.62 was obtained from the 15 positive results. Both IEF and DCC methods can measure receptor concentrations as low as 5 femtomoles/mg protein; however, the IEF results were obtained on as little as 1/10th the amount of material. (12 Refs)

34. ASSAY OF ESTRADIOL RECEPTORS IN HUMAN BREAST CARCINOMAS USING THE GAMMA EMITTING LIGAND 16ALPHA[125I]IODOESTRADIOL.

Duffy MJ

Dept. Nuclear Medicine, St. Vincent's Hosp., Dublin 4, Ireland

J Steroid Biochem; 16(2):343-344 1982

The use of 16alpha[125I]iodoestradiol to assay estrogen receptor (ER) in human breast carcinoma was investigated. A constant amount of cytosol was incubated at five different concentrations of radiolabeled estradiol overnight at 4 C, and nonspecific binding was measured with parallel incubations in the presence of 100-fold excess unlabeled diethylstilbestrol (DES). Excess unlabeled estradiol and DES were the most potent inhibitors of binding, estrone and estriol were less potent, and testosterone, progesterone, and cortisol were ineffective. The affinity of iodoestradiol for breast tumor ER was similar to that of tritiated estradiol in 19 carcinoma cytosols. Good agreement was found between results using tritiated and iodoestradiol as ligands (correlation coefficient = 0.97). Twelve tumors contained less than 50 femtomoles ER by both ligands. Good agreement was observed between the use of a single saturating concentration of 5 nanoM iodoestradiol and the Scatchard plot analysis using the same ligand (correlation coefficient = 0.97). Advantages of using a gamma-emitting ligand for the assay of ER in breast tumor tissue are listed. (4 Refs)

35. IMMUNOHISTOCHEMICAL LOCALIZATION OF ESTROGEN RECEPTORS IN HUMAN MAMMARY CARCINOMA USING ANTIBODIES TO THE RECEPTOR PROTEIN.

Raam S, Nemeth E, Tamura H, O'Briain DS, Cohen JL
Oncology Lab., Tufts Univ. Medical Cancer Unit, Lemuel Shattuck Hosp., 170 Morton St., Boston, MA, 02130
Eur J Cancer Clin Oncol; 18(1):1-12 1982

An immunofluorescent method has been developed for localizing estrogen receptors (ER) in frozen sections of human breast cancer biopsies which utilizes the biochemically well-characterized antibodies to the cytoplasmic ER of human breast cancer produced in rabbits. Frozen sections of 16 breast cancer biopsies, in which the receptor content has been quantified using dextran-coated charcoal assay (DCC technique), were used to study the localization of ER. Two aspects of ER detection, namely 'estrogen-binding' and ability to react with the homologous antibodies, have been analyzed and the results compared with those of DCC technique. Fluorescent labeled estrogen method (F-E2) of Pertschuk was utilized to detect the distribution of estrogen binding proteins and the indirect immunofluorescent (IM-AR) method using antireceptor antibodies to assess the antigenic sites of the receptor protein. In addition to the comparison of the results of three techniques, DCC, IM-AR and F-E2, for ER detection, a procedure for processing the frozen sections, which enables the study of estrogen binding characteristic as well as the antigenic reactivity of the receptor molecules, is described. (Author abstract) (10 Refs)

36. ASSOCIATION OF PLASMINOGEN ACTIVATOR ACTIVITY AND STEROID RECEPTORS IN HUMAN BREAST CANCER.

Thorsen T
Hormone Lab., Univ. Bergen Sch. Medicine, Bergen, Norway
Eur J Cancer Clin Oncol; 18(2):129-132 1982

Plasminogen activating activity (PAA) has been determined in 105 human breast cancer cytosols with a colorimetric assay. PAA has been related to steroid receptors in the same cytosols. A strong positive correlation between PAA and progesterone receptor levels was found (Spearmans coefficient of rank correlation, $R = 0.74$, p less than 0.001). PAA discriminates between progesterone receptor-positive and -negative tumors, irrespective of estradiol receptor content. It is suggested that PAA is a marker of functional estradiol receptor and that fibrinolytic activity may be a causative factor in the low metastatic potential of progesterone receptor-positive tumors. (Author abstract) (25 Refs)

37. MICROASSAY OF HORMONAL RECEPTORS BY NEEDLE BIOPSY IN HUMAN BREAST LESIONS AND TUMORS. DETERMINATION OF ESTROGEN RECEPTORS.

Delarue JC, Mouriesse H, Contesso G, May-Levin F, Sancho-Garnier H
Institut Gustave-Roussy, Rue Camille-Desmoulin, 94800 Villejuif, France
Biomedicine; 34(3):153-160 1981

Estrogen receptors measurement was assayed in human mammary tumors as well as corresponding fine needle aspiration biopsies (95 cases). Correlations between these two determinations were highly significant just as correlations between aspiration biopsies of the same tumor. Some factors may disturb the quality of aspiration biopsy results particularly: a low number of tumoral cells expressed by the cell density, ratio: sample weight-cytosol volume lower than 1/17 corresponding to a too great dilution, a sample weight lower than 20 mg. (Author abstract) (13 Refs) (In FRE)

38. RESEARCH ON ESTROGEN AND PROGESTERONE RECEPTORS IN HUMAN BREAST CANCER.

Kakuta E

Second Dept. Surgery, Tokushima Univ. Sch. Medicine, Tokushima-shi, Japan

Nippon Gan Chiryo Gakkai Shi; 16(7):1408-1416 1981

Estrogen receptors (ER) and progesterone receptors (PR) were measured with the aid of gel-filtration in the cytosols of human breast cancer tissues from 120 patients with primary breast cancer and 32 with recurrent breast cancer. The ER and PR were measured at the same time in surgical specimens from 53/120 patients with the primary cancer and 22/32 with the recurrent cancer. ER were present (ER+) in 43.1% of the cases and PR were present (PR+) in 25%. Differences in the frequencies of ER+ and PR+ were not related to the stage or histological type of the cancer or to the pre- or postmenopausal status of the patients. PR+ findings were observed significantly more often in tissues that were also ER+ than in those that were ER negative (ER-). Results indicating the presence or absence of ER and PR in primary and metastatic tumor nests were often consistent whether or not ER and PR were measured synchronously. Effectiveness of endocrine therapy was observed in 71.4% of the ER+ patients, 5.6% of the ER-, 4/5 PR+, and 3/14 PR-. It was concluded that selection of patients who are likely to have effective endocrine therapy for breast cancer may be enhanced by measuring ER in breast cancer tissues. (23 Refs) (In JPN)

39. CELLULAR LOCALIZATION OF ESTROGEN BINDING SITES IN HUMAN BREAST CANCER.

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Am J Clin Pathol; 77(4):391-395 1982

Biopsy specimens from 52 consecutive cases of primary human breast cancer were collected over a period of 7 mo and included in a study for histochemical localization of estrogen binding sites (EBS), using a fluorescein labeled Estradiol conjugate. Cryostat frozen sections from each tumor were examined to determine the localization of the tracer and to evaluate the percentage of positive cells in a given tumor. Results are correlated with the values of the biochemical assay for the estrogen receptor (ER) protein done on the same tumor. The localization of EBS by a tracer is a simple technique that can be done and interpreted in any surgical pathology laboratory. It was concluded that this method could be a valuable supplementary technique to the biochemical assay; allowing more accurate selection of patients and prediction of their response to endocrine therapy. Clinical follow-ups are extremely necessary to evaluate the suitability and the accuracy of the technique in choosing breast cancer patients for endocrine manipulation. (Author abstract) (17 Refs)

40. ESTROGEN AND PROGESTERONE RECEPTORS IN TUMORS OF THE HUMAN OVARY.

Hahnel R, Nat R, Kelsall GR, Martin JD, Masters AM, McCartney AJ, Twaddle E

Dept. Obstetrics and Gynaecology, Univ. Western Australia, Subiaco, 6008, Australia

Gynecol Oncol; 13(2):145-151 1982

A total of 23 malignant ovarian tumors and 5 benign or tumor-like lesions of the ovary had their estrogen receptor (ER) status, and of these 15 also had their progesterone receptor (PR) status, determined. Tumors were said to be ER+ when the receptors bound greater than 4 fmole estradiol/mg protein and PR+ when they bound greater than 10 fmole progesterone/mg protein. Ten of 22 ovarian carcinomas were estrogen receptor positive (ER+) and 3 of these also contained progesterone receptors (PR+). All six malignant ovarian tumors occurring in premenopausal women were ER- and PR- as were the two benign tumors occurring in two premenopausal patients. It may be that premenopausal women have tumors which are more frequently ER- PR- because their higher blood hormone levels block the estrogen and progesterone binding sites in the tissues. It was not possible to show any variation from normal in the plasma hormone levels (estradiol, estrone, testosterone, progesterone, FSH). It is suggested that hormone receptor studies of malignant ovarian tumors could aid in the selection of patients suitable for therapies based on endocrine manipulation. (Author abstract) (15 Refs)

41. PROGESTERONE RECEPTOR IN GRANULOSA CELL TUMOR.

Meyer JS, Rao BR, Valdes R, Burstein R, Wasserman HC

Dept. Pathology, The Jewish Hosp. St. Louis, St. Louis, MO, 63178

Gynecol Oncol; 13(2):252-257 1982

A virilizing granulosa cell tumor of the ovary contained large amounts of testosterone and progesterone and small amounts of estrogens. Assays for progesterone receptor were positive, but estrogen receptor could not be detected. The presence of progesterone receptor in the tumor is consistent with recent evidence for a role of the receptor in the physiology of the Graafian follicle, and suggests the possibility that progestational therapy may be effective in advanced stage granulosa cell tumor. (Author abstract) (23 Refs)

42. NEW STEROIDAL NITROSOUREAS.

Chavis C, De Gourcy C, Borgna JL, Imbach JL

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Steroids; 39(2):129-147 1982

Seventeen beta and 20 nitrosourea derivatives belonging to the dehydroepiandrosterone, estrone and pregnenolone series have been synthesized. The behavior of these compounds towards the calf uterine estradiol and pregnenolone receptors have been studied. (Author abstract) (29 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

43. ULTRACYTOCHEMICAL LOCALIZATION OF ESTROGEN-STIMULATED GUANYLATE CYCLASE IN RAT UTERUS.

Kang YH, Sahai A, Criss WE, West WL
Dept. Pathology, USUHS, Bethesda, MD, 20814
J Histochem Cytochem; 30(4):331-342 1982

Estrogens are known to increase cyclic guanosine monophosphate (cGMP) levels in the uterus of rats by enhancing guanylate cyclase (GC) activity. In the present study, the cytochemical localization of GC activity was studied in the uteri of immature and ovariectomized rats after treatment with diethylstilbestrol (DES), progesterone, estrogen antagonist (C1628), and a combination of DES and C1628. Twenty-four hr after the first dose of DES, moderate to strong guanylate cyclase activity was indicated by lead phosphate precipitate on the luminal microvillar and basolateral surfaces of epithelial cells, whereas strong activity was found on the plasma membranes of fibroblasts, endothelial cells, and myometrial cells. The enzyme activity in the epithelial cells declined slightly 24 hr after the second daily dose of DES. Uterine tissues from DES-treated rats that were preheated at 60 C for 30 min or preincubated with a GC inhibitor showed no reaction product. Guanylate cyclase activity was not observed cytochemically in the uterine tissues of the vehicle control (immature or ovariectomized) or progesterone- and C1628-treated animals. Weak guanylate cyclase activity was observed on the plasma membranes of epithelial cells and endothelial cells after doses of DES and C1628 were given simultaneously. The biochemical assays of the total homogenate in vitro indicated that uterine GC showed about a twofold increase after one dose of DES and a 1.3-fold increase following two doses (1 dose per day) of DES when compared with their respective nontreated controls, or with progesterone-treated uteri. GC was found in particulate (90%) and cytosol (10%) fractions. These data demonstrated that DES stimulated uterine guanylate cyclase activity, while progesterone and C1628 were ineffective at the doses used. Estrogen antagonist C1628 does not completely suppress the effect of DES. (Author abstract) (38 Refs)

44. PREVENTION OF THE IN VITRO MYELOSUPPRESSIVE EFFECTS OF GLUCOCORTICOSTEROIDS BY INTERLEUKIN 1 (IL 1).

Mishell RI, Lee DA, Grabstein KH, Lachman LB
Dept. Microbiology and Immunology, Univ. California, Berkeley, CA, 94720
J Immunol; 128(4):1614-1619 1982

We investigated the effects of dexamethasone on the formation of granulocyte/macrophage colonies by murine bone marrow cells cultured with colony-stimulatory factors (CSF) in semisolid agar. Dexamethasone (10-7M) completely inhibited the formation of colonies in response to L929 CSF but had no effect on the response to CSF in the culture supernatants of the murine macrophage cell line, PU5-1.8. We postulated that a cofactor, interleukin 1, present in the PU5-1.8 supernatants was responsible for protecting colony formation against steroid suppression. Interleukin 1, isolated from culture supernatants of PU5-1.8 and from culture supernatants of human acute monocytic leukemia cells, blocked the inhibitory effects of dexamethasone on colony formation in response to L929 CSF. Moreover, dexamethasone inhibited colony formation in response to PU5-1.8 culture supernatants when interleukin 1 was absent. We also examined interleukin 2 for possible protective effects. Although crude interleukin 2 preparations (supernatants of spleen cells cultured with concanavalin A) blocked dexamethasone inhibition, purified interleukin 2 had no protective effects. These data indicate that interleukin 1 protects colony formation by a pathway that is independent of interleukin 2 and that supernatants of spleen cells activated with concanavalin A probably contain significant amounts of interleukin 1. (Author abstract) (64 Refs)

45. INFLUENCE OF ESTRADIOL ON THE TOTAL UPTAKE AND INCORPORATION OF THYMIDINE IN HUMAN BREAST CANCER (MCF-7) IN LONG-TERM CELL CULTURE: COMPARISON OF AUTORADIOGRAPHIC AND BIOCHEMICAL METHODS.

Coosen R, De Jong PW, Schwarz F
Dept. Endocrinology, Univ. Hosp., 3511 GV Utrecht, The Netherlands
Mol Cell Biochem; 42(3):155-160 1982

The total uptake and incorporation into DNA of 3H-thymidine in MCF-7 cells is stimulated by estradiol after an incubation period of 24 hr. Prolonged incubations show a decreased rate of both uptake and incorporation of 3H-thymidine, but the labeling index remains elevated up to 48 hr. It appears that this is the only exception to the observed good relationship between labeling index and total uptake of 3H-thymidine. This correlation may be of use in comparing autoradiographic and biochemical data on DNA synthesis in the case of culturing both primary mammary tumors and mammary cancer cell lines. (Author abstract) (22 Refs)

46. IN VIVO AVAILABILITY OF CIRCULATING ESTRADIOL IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT ENDOMETRIAL CANCER.

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Obstet Gynecol; 59(4):416-421 1982

To assess the in vivo effect of plasma proteins on the tissue availability of circulating estradiol in postmenopausal women with endometrial cancer, the transport of tritiated estradiol across the brain capillary wall, ie, the blood-brain barrier, was examined in anesthetized rats using a tissue sampling-single injection technique. Serum samples were studied from 25 women with endometrial cancer and from an equal number of women without the disease who were matched to the cancer patients for age and percent ideal wt. The mean +- SE brain uptake indices of estradiol, using serum from the cancer patients and controls, were 40.7 +-2.8 and 33.9 +-2.6, respectively. This difference was not statistically significant. Positive correlations were observed between the brain uptake index and percent ideal wt in the cancer ($r = 0.65$) and in the control ($r = 0.21$) subjects. Linear regressions of the reciprocal of the brain uptake index and levels of sex hormone-binding globulin showed strong correlations ($r = 0.78$) in both groups of patients, whereas correlation coefficients between the brain uptake index and percentage sex hormone-binding globulin were $r = 0.86$ and $r = 0.98$ for the cancer and the control subjects, respectively. These latter observations support the concept that the brain uptake index reflects the effects of plasma proteins on transport of estradiol across a capillary wall. The findings of this study indicated that (1) the fraction of estradiol available for transport across the blood-brain barrier greatly exceeded the free (dialyzable) moiety and was essentially equal to the albumin-bound and free (dialyzable) fractions of the plasma hormone; and (2) the tissue availability of estradiol was influenced by the body size of the subjects, particularly in the cancer patients, with more circulating estradiol being available in the obese women. This observation suggests that obese, older women are at dual risk of the action of estradiol at the tissue level. They have higher total levels and proportionately greater bioavailable fractions than slender subjects. (Author abstract) (24 Refs)

47. HORMONAL REGULATION OF NET DNA SYNTHESIS IN MCF-7 HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

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Cancer Res; 42(5):1727-1735 1982

Estrogens and anti-estrogens have striking effects on growth of target tissues in vivo. In order to examine these effects in vitro, experimental methods for the rigorous assessment of rates of net DNA synthesis in tissue culture systems are required. The quantitation of DNA synthesis with inorganic [32P]orthophosphate is described. The limitations of more conventional [3H]thymidine labeling are illustrated in this hormonally responsive system. Estrogen administration increases the specific activity of acid-soluble phosphate and increases net DNA synthesis relative to controls in MCF-7 human breast cancer cells. Stimulation is most evident after 36 hr of hormone treatment. Conversely, tamoxifen produces substantial inhibition of net DNA synthesis after 36 hr of hormone treatment. Thymidine availability modulates the effect of estrogens and anti-estrogens on DNA synthesis and constitutes an independent experimental variable. (Author abstract) (55 Refs)

48. THE EFFECT OF CATECHOLESTROGENS ON THE GROWTH OF PROLACTIN-SECRETING PITUITARY TUMORS AND NORMAL PROLACTIN SYNTHESIS IN THE RAT.

Lamberts SW, Nagy I, Uitterlinden P, MacLeod RM
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Endocrinology; 110(4):1141-1146 1982

The effects of the catecholestrogens 2-hydroxyestrone (2-OHE1) and 2-hydroxyestradiol (2-OHE2) on the growth of the estrogen-induced transplantable PRL-secreting rat pituitary tumor 7315a were compared with the effects produced by the chronic administration of estradiol (E2) and estriol (E3). 2-OHE2 (100 ug/kg/day for 27 days) inhibited pituitary tumor growth by 38 +-8% (p less than 0.05), while producing no change in the weight and total PRL content of the pituitary gland. It exerted a small uterotropic effect in tumor-bearing rats and impaired body growth slightly. 2-OHE1 (100 ug/kg/day) inhibited pituitary tumor growth by 56 +-9% (p less than 0.01) and suppressed both the weight (p less than 0.01) and the total PRL content of the pituitary gland (p less than 0.01). The compound normalized the weight of the uterus and did not influence body growth. Both E2 (20 ug/kg/day) and E3 (100 ug/kg/day) profoundly inhibited pituitary tumor growth (-98 +-3 and-83 +-6%, respectively; p less than 0.01 and p less than 0.01, respectively). These steroids had a strong positive effect on the pituitary PRL content and the pituitary, ovarian and uterine weights, while they significantly suppressed body growth. The effect of 2-OHE2 on synthesis and release of PRL by the normal pituitary gland was studied. 2-OHE2 (20 ug/day for 6 days) exerted a positive effect on PRL synthesis and release by male rats, which was additive to that of E2. In normal female rats, however, no effect of 2-OHE2 administration (25 ug/day for 4 days) was noticed, while it counteracted the positive effect of E2 completely. 2-OHE1 and 2-OHE2 inhibit pituitary tumor growth via a mechanism which is different from that of high concentrations of E2 and E3. 2-OHE1 exerted a strong antiestrogenic action on tumor growth and normal PRL synthesis, while the effects of 2-OHE2 on normal PRL synthesis and release seem to be estrogenic or antiestrogenic, depending on the estrogen status of the animal. (Author abstract) (29 Refs)

49. GLUTAMINE SYNTHETASE INDUCTION BY GLUCOCORTICOIDS IN THE GLUCOCORTICOID-SENSITIVE HUMAN LEUKEMIC CELL LINE CEM-C7.

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J Cell Physiol; 110(2):155-160 1982

Glucocorticoid stimulation of glutamine synthetase (GS) was studied in the glucocorticoid-sensitive human leukemia cell line CEM-C7. When cells were grown in the presence of 10(-6) M dexamethasone (DEX) for various time periods and then assayed for GS activity, after a lag of 1-2 hr, enzyme activity increased 2.0-2.5-fold to a value of approx 4.5 x 10(-2) micromoles/min/mg. This effect was max after 12 hr of DEX treatment. The relationship of GS activity to steroid concentration was determined by incubating cells with various concentrations of DEX for 18 hr. Half-max GS response was obtained with 2 x 10(-8) M and max response with 2 x 10(-7) M DEX. Direct proof that GS elevation is a receptor-mediated phenomenon was obtained by examining the response of GS induction in a subclone of CEM-C7 (ICR-27) that contains no glucocorticoid receptor. At concentrations of 2 x 10(-7) M, DEX elicited maximal GS response, whereas prednisolone and cortisol, less potent glucocorticoids, elicited correspondingly lower responses. The inactive glucocorticoid cortexolone and the nonglucocorticoids progesterone, 17-beta-estradiol, and 5-alpha-dihydrotestosterone produced no elevation in GA activity demonstrating that GS induction in CEM-C7 cells is a glucocorticoid-specific response. GS synthesis required RNA and protein synthesis and the continued presence of of a glucocorticoid. Increased GS activity induced by DEX did not appear to result from glutamine deprivation. In contrast to its antagonism of GS induction, bromodeoxyuridine did not interfere with the ability of DEX to inhibit growth in CEM-C7 cells. (34 Refs)

50. HORMONE-DEPENDENT MATURATION OF MAJOR STRUCTURAL PROTEINS OF MURINE MAMMARY CANCER VIRUS.

Beriashvili MM, Chernova OB, Kolobkov SL, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vopr Virusol; (1):34-38 1982

The effects of hormones on the processing of major structural proteins of murine mammary cancer virus (MMCV) were studied in virus-producing cells of mammary gland carcinoma of IK mice. Expression of the virus-specific products was assayed by radioimmunoprecipitation technique. Celles cultured in the hormone-free medium showed an expression of the products of gag and env genes. Incubation of cells with insulin and with dexamethasone resulted in marked stimulation of the processing of major glycoprotein of the virion envelope (gPr 70env). (10 Refs) (In RUS)

51. PARADOXICAL EFFECTS OF GLUCOCORTICOIDS ON REGULATION OF PLASMINOGEN ACTIVATOR ACTIVITY OF RAT HEPATOMA CELLS.

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Dept. Human Genetics and Internal Medicine, Univ. Michigan Medical Sch., Ann Arbor, MI, 48109
Proc Natl Acad Sci USA; 79(7):2319-2322 1982

Incubation of rat hepatoma cells with cAMP derivatives stimulates cell-associated plasminogen activator activity 8-to 22-fold and extracellular plasminogen activator activity 30-to 1,300-fold. This time- and concentration-dependent increase is enhanced by phosphodiesterase inhibitors. Dexamethasone, a synthetic glucocorticoid, decreases the plasminogen activator activity of these cells, probably through induction of an inhibitor. Paradoxically, dexamethasone, added simultaneously with cAMP derivatives causes a further four-fold enhancement of the cAMP-mediated stimulation of plasminogen activator activity. Dexamethasone also alters the time course of cAMP-mediated enhancement of plasminogen activator activity: increased protease activity is detected at 4 hr in cells incubated with 8-bromoadenosine-3':5'-cyclic monophosphoric acid and 1-methyl-3-isobutylxanthine but not until 12 hr in cells incubated with dexamethasone as well. Glucocorticoids thus exert two separate and opposite effects on plasminogen activator activity: induction of an inhibitor and amplification of cyclic nucleotide action. Although permissive and synergistic effects of dexamethasone on cyclic nucleotide action have been reported previously, glucocorticoid regulation of plasminogen activator activity is unique in that the amplification of cyclic nucleotide effects by dexamethasone opposes its regulatory action toward a specific enzyme. (Author abstract) (35 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

52. ACTIVITY OF 3BETA-HYDROXY-13ALPHA-AMINO-13,17-SECO-5-5A-1 ANDROSTANE-17-OIC-13,17-LACTAM(P-(BIS(2 CHLOROETHYL)AMINO)-PHENYL)ACETATE (NSC 290205) IN MURINE SOLID TUMORS.

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Oncology; 39(2):109-112 1982

The modified steroidal alkylating agent, 3beta-hydroxy-13alpha-amino-13,17-seco-5alpha androstane-17-oic-13,17-lactam[p-[bis(2 chloroethyl)amino]-phenyl]acetate showed excellent activity in treatment of three murine solid tumors. Colon 26-bearing CD2F1 mice lived twice as long as controls with tumor free survivors at the end of the 70-day observation period. CD8F1 mammary tumor growth was suppressed greater than 90% compared to controls. B16 melanoma-bearing B6D2F1 mice lived 50% longer than controls. This agent had previously been shown to be active in treatment of the Theagenion-Bahner angiosarcoma, the T8 Guerin tumor, L1210 leukemia and P388 leukemia. (Author abstract) (26 Refs)

53. AN ANALYTIC CELLULAR EVALUATION OF ASPIRATED SMEARS FROM TRANSPLANTED HUMAN ENDOMETRIAL ADENOCARCINOMA IN NUDE MICE TREATED WITH 17BETA-ESTRADIOL AND PROGESTERONE.

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Acta Cytol (Baltimore); 26(2):251-258 1982

The effects of 17beta-estradiol and progesterone on human endometrial adenocarcinomas grafted into BALB/c nude mice were studied. Cytologic studies were made on aspiration biopsy smears obtained from the grafts with a fine needle. Mitotic figures were frequently observed in the cells obtained from 17beta-estradiol-treated mice, whereas there were few mitotic figures in cells from progesterone-treated ones. Progesterone produced such morphologic changes as multinucleolation and cytoplasmic vacuolization. Untreated tumors and those treated with 17beta-estradiol were solid and were interpreted as poorly differentiated adenocarcinomas. Progesterone-treated tumors were slightly soft but were also interpreted as poorly differentiated adenocarcinomas; however, central necrosis was seen frequently, and differentiation occurred at the margin of these tumors. 17beta-estradiol promoted increased tumor growth, whereas progesterone produced differentiation and inhibited tumor growth. (Author abstract) (18 Refs)

54. MORPHOLOGICAL ALTERATIONS OF BASAL CELLS OF VAGINAL EPITHELIUM IN NEONATALLY OESTROGENIZED MICE.

Mori T, Nishizuka Y
Zoological Inst., Faculty of Science, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan
Experientia; 38(3):389-390 1982

Neonatal estrogen treatment results in the development of vaginal cancers in the mouse. A morphological sign which probably indicated early invasion of altered vaginal cells into the stroma through gaps in the basal lamina was first seen at 10 months of age in neonatally estrogenized C57Black mice. Prior to this, a decrease in the numbers of cellular attachment organelles such as half desmosomes and desmosomes was observed by 3 months. (Author abstract) (12 Refs)

55. ROLE OF ESTROGENS AS PROMOTERS OF HEPATIC NEOPLASIA.

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Dept. Pathology, Toronto Western Hosp., Toronto, Ontario, Canada
Lab Invest; 46(3):313-320 1982

The administration of estrogens to humans has been associated with the development of benign and possibly malignant hepatocellular neoplasms. This study was designed to investigate the mechanism of this association. We present a rat model that demonstrates that stilbestrol (DES) and ethinyl estradiol promote the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Eighty male and 12 female Fischer-344 rats were given a single intraperitoneal injection of either DEN (200 mg/kg of body wt) or saline. Beginning 4 wk after injection, the rats were given an estrogen or corn oil twice weekly for up to 50 wk. Treatments were stopped at the time of sacrifice or 11 to 29 wk prior to sacrifice. Estrogen treatments included high dose DES (5 mg per dose), low dose DES (0.5 mg per dose), and ethinyl estradiol (0.2 mg per dose). Male and female rats given both DEN and high dose of DES developed grossly visible hepatic hyperplasic nodules (mean, 9.1 per liver) after 20 wk of DES. Nodules also developed if the onset of DES treatment was delayed until 28 wk after initiation. Rats given DEN alone or DES alone did not develop nodules after 20 wk. Microscopic hyperplastic foci also developed in rats given DEN plus DES, DES alone, and DEN alone. The foci in rats given DES alone were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinyl estradiol was observed. Low dose DES was not effective in promoting tumor formation. The data indicate that estrogens promote hepatic neoplasia, perhaps by increasing hepatocyte mitotic activity and thereby facilitating the evolution of previously initiated cells into neoplastic clones. Comparison with human disease should be made with caution, especially because the estrogenic dose administered was approx 200-fold the usual contraceptive dose in humans. However, the analogy between this model and the development of human oral contraceptive-associated hepatic tumors is evident. It is possible that some women have latent 'initiated' cells that divide faster than the surrounding hepatocytes in response to estrogens. (Author abstract) (29 Refs)

56. ON THE ROLE OF ESTROGENS IN ENDOMETRIAL CARCINOGENESIS.

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Dept. Obstetrics and Gynecology, Univ. Hosp., S-221 85 Lund, Sweden
Acta Obstet Gynecol Scand [Suppl]; (106):33-35 1981

The role of estrogen in endometrial carcinoma as a carcinogenic agent or as a promoter is discussed. Dosage level, duration of treatment, and formula of preparations must be considered when investigating the role of estrogens in development of endometrial cancer. The observation that the risk declines after cessation of estrogen treatment argues for a promoter effect of estrogens. The antipromoter effect of progestogens is discussed. (30 Refs)

57. ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF ENDOMETRIAL AND BREAST CANCER.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Acta Obstet Gynecol Scand [Suppl]; (106):37-46 1982

Although there is a slightly increased risk of endometrial cancer from estrogen therapy for menopausal women, progestogens given along with the estrogen significantly decrease the incidence of this malignancy to a rate lower than that of untreated women. Postmenopausal women predisposed to adenocarcinoma of the endometrium because of increased endogenous estrogens can be identified with the progestogen challenge test and treated with cyclic progestogens for 10 days each mo to prevent endometrial cancer. Oral contraceptives containing both estrogens and progestogens in each tablet are protective against developing adenocarcinoma of the endometrium, whereas the sequential birth control pills provided less protection. The incidence of breast cancer is significantly lower in both estrogen and estrogen-progestogen users than in postmenopausal women never using these hormones. In those women found to have breast cancer while using these hormones, the prognosis is better than that found in women never exposed to exogenous estrogens, most likely due to an earlier detection. No clear-cut pattern of either abnormal hormone production or milieu has been found in women with carcinoma of the breast. Oral contraceptives reduce the risk of benign breast disease and afford some protection from the subsequent development of breast cancer. The mortality rate from breast cancer developing in oral contraceptive users is significantly lower than that of the non-users. (Author abstract) (50 Refs)

58. EMBOLIZATION, POLYCHEMOTHERAPY, AND HORMONE THERAPY IN THE TREATMENT OF METASTASIZED RENAL CARCINOMA.

Amorosi W, Fiore M, Ingrosso D, Panza N, Campanella L, Carteni G, Spena A, Cataldo B
Divisione di ChemioterapiaAntiblastica Generale - Osp. 'A. Cardarelli', Ente Ospedaliero Regionale Generale - Ospedali Riuniti di Napoli, Napoli, Italy
Rass Int Clin Ter; 61(12):805-811 1981

A 67-yr-old man, who underwent laryngectomy due to cancer 7 yr ago, had hematuria. After urography, arteriography, radiography, cytologic examination of urine, and chest stratigraphy, a diagnosis of inoperable renal adenocarcinoma with pulmonary metastases (PM) was established. Embolization of renal artery with spongostan, polychemotherapy (adriamycin, VM26, and lomustine), and hormone therapy (medroxyprogesterone) was administered. After 1 yr the PM had disappeared and after 56 mo the patient was still alive. (23 Refs) (In ITA)

59. ONCOLOGICAL ASPECTS OF SCLEROCYSTIC OVARY SYNDROME.

Bokhman IaU, Vishnevskii AS, Umenushkina LN, Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Akush Ginekol (Mosk); (2):19-21 1982

Role of sclerocystic ovary syndrome (SCOS) in the etiology of hyperplasia and cancer of the endometrium is discussed. Development of hyperplastic changes in the endometrium is associated with enhanced estrogenic stimulation of the uterine mucosa. It was recommended to include the patients with all variants of SCOS into high risk group. The patients with SCOS should undergo two-stage treatment consisting of progestagen and agents that stimulate ovulation and normalize the menstrual cycle. (5 Refs) (In RUS)

60. MONOCHEMOTHERAPY (ADRIAMYCIN) FOR METASTATIC BREAST CANCER IN PROGRESSION AFTER SEQUENTIAL HORMONE-CHEMOTHERAPY (MAP AND CMF): PILOT STUDY.

Pannuti F, Rossi AP, Di Marco AR, Fruet F, Lelli G, Strocchi E, Rocchetta G, Piana E, Martoni A
Divisione Oncologica, Ospedale 'M. Malpighi', Via Albertoni 15, 40138 Bologna, Italy
Panminerva Med; 23(1):25-28 1981

Twenty postmenopausal patients with metastatic breast cancer no longer responsive to sequential hormone-chemotherapy (Medroxyprogesterone Acetate at high doses, MAP, and cyclophosphamide + Methotrexate + 5-Fluorouracil, CMF), were treated with Adriamycin (Adria) alone (80 mg/m2/iv/21 days). Eight patients (40%) responded with a greater than 50% regression of measurable tumor The median duration of response was 5 mo (range 1-8) and of survival 17 mo (range 2-23+) for responders and 10 mo (range 3-22) for nonresponders (significant statistical difference, p less than 0.05). Adria is effective on patients with grossly metastatic disease relapsing after prior sequential hormone-chemotherapy. Remission rates are very close to those achievable both with Adria and with many polychemotherapy regimens in previously untreated patients. (Author abstract) (16 Refs)

61. REGRESSION OF PITUITARY MICROADENOMA DURING AND FOLLOWING BROMOCRIPTINE THERAPY: PERSISTENT DEFECT IN PROLACTIN REGULATION BEFORE AND THROUGHOUT PREGNANCY.

Yuen BH, Cannon W, Sy L, Booth J, Burch P

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Am J Obstet Gynecol; 142(6,part1):634-639 1982

During 5 yr of clinical, endocrinologic, and radiologic observations in a woman with a microprolactinoma treated medically with bromocriptine for 29 mo, serial hypothalamic-pituitary studies revealed a defect in lactotrope function after prolactin (PRL) concentrations and ovulation were restored to normal. This defect persisted throughout a spontaneously conceived pregnancy in which the PRL, estradiol, and progesterone levels were subnormal, while the dehydroepiandrosterone sulfate levels were normal and estriol concentrations were elevated. Levels of the beta subunit of human chorionic gonadotropin (hCG) were close to and slightly above the normal ranges. These observations are consistent with a role for PRL, interacting with hCG, in the control of estrogen and progesterone secretion by the fetoplacental unit. Lactation was initiated and maintained post partum. Pituitary function and PRL responses to suckling suggested improved lactotrope function 22 to 25 mo after withdrawal of bromocriptine. The impaired lactotrope function, therefore, did not preclude normal implantation, pregnancy maintenance, onset of parturition, fetal development, and lactation. (Author abstract) (19 Refs)

62. TAMOXIFEN AND AMINOGLUTETHIMIDE IN THE MANAGEMENT OF PATIENTS WITH ADVANCED ENDOMETRIAL CARCINOMA NOT RESPONSIVE TO MEDROXYPROGESTERONE.

Quinn MA, Campbell JJ, Murray R, Pepperell RJ

Dept. Obstetrics and Gynaecology, Univ. Melbourne, Melbourne, Australia

Aust NZ J Obstet Gynaecol; 21(4):226-229 1981

Eleven (58-74-yr old) females with recurred endometrial adenocarcinoma were treated for 8 wk with tamoxifen (T: 20 mg/d, bid) or aminoglutethimide (AG: 250 mg/d, bid; 250 mg/d increase every 2 days) until adrenal blockade effected reduction of plasma dehydroepiandrosterone sulfate to at least 50% of base line value. Cortisone acetate and fluorocortisone were used as replacement therapy. The second drug was added after the 8 week evaluation only when response was progression, regardless of T or AG being first. A partial or complete initial response resulted in indefinite continuation of initial therapy with monthly review, or until progression resumed. Toxic effects included nausea from T sufficient to change treatment to AG in two subjects, lethargy common from AG, and intermittent dizziness in two subjects from AG. Details of six cases are presented. Both drugs are indicated to be useful in subjects resistant to medroxyprogesterone. (37 Refs)

63. EFFECT OF MEDROXYPROGESTERONE ACETATE ON DMBA-INDUCED RAT MAMMARY CARCINOMA AND ON IMMUNOLOGICAL REACTIVITY.

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Eur J Cancer Clin Oncol; 18(1):45-51 1982

The antineoplastic activity of medroxyprogesterone acetate (MPA) was investigated in rats bearing DMBA-induced mammary carcinomas, a classical model of hormone-dependent tumor. Using a repeated injection schedule of relatively short duration, MPA was markedly effective (80% CR + PR) not only on relatively small (1-1.5 cm) tumors but also on advanced (4.5-5.5 cm) neoplasms. MPA effectiveness was comparable to that of a frankly toxic adriamycin regimen. In antitumorally effective schedules MPA was incapable of significantly affecting in either direction cellular and humoral immunological reactivities in rodents. (Author abstract) (23 Refs)

64. EFFECTS OF ESTROGENS AND ANTIESTROGENS ON ANDROGEN-DEPENDENT GROWTH OF SHIONOGI CARCINOMA 115: ROLE OF ESTROGEN RECEPTOR.

Nohno T, Omukai Y, Watanabe S, Saito T, Senoo T

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Cancer Lett; 15(3):237-244 1982

The effects of estrogens and antiestrogens on Shionogi carcinoma 115 (SC115) tumor growth in relation to the receptor binding of androgen or estrogen were examined. Male DS mice (6-18 wk old) were used. Castration was performed 3 days prior to drug treatment. The growth of SC115 was dependent on androgens. Cumulative lethal takes were evaluated on day 60, and were 352 of 367 (96%) in males and 13 of 102 (13%) in females. When estradiol (ES) or diethylstilbestrol (DES) was given to intact male mice at a daily dose of 2 mg/kg, TG as well as the wt gains of seminal vesicles (SV) and prostate glands was inhibited. TG was stimulated with 5 mg/kg nitromifene. Consistent decrease in tumor wt was observed in intact animals after administration of 0.5-50 mg/kg tamoxifen (TX). In the castrated mice (CM) given 4 mg/kg of testosterone propionate from day 0, 5 mg/kg of TX had no effect on TG but 20 mg/kg TX slightly increased the tumor wt. The wt of SV decreased at the higher dose of TX. Androgen receptors (AR) in the tumor cytosol of androgen-treated CM were 32.5 +-5.5, 28.9 +-6.3, and 39.3 +-8.2 femtomole/mg protein at TX doses of 0, 5, and 20 mg/kg, respectively. No remarkable change in histology of SC115 was observed when estrogens and antiestrogens affected the TG. ES competed effectively for [3H]dihydrotestosterone (DHTT) binding but DES and TX did not. DES in 100-fold molar excess did not maximally inhibit [3H]ES binding to SC115 cytosol and low concentrations of DHTT effectively decreased a fraction of [3H]ES binding. Results indicated that ES most likely binds not only to ER but also to AR in the tumor cytosol. (17 Refs)

65. A COMPARISON OF THE EFFICACY FOR ANTITUMOR ACTIVITY OF THE NON-STEROIDAL ANTIESTROGENS ANALOG II AND TAMOXIFEN IN 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY TUMORS.

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Cancer Lett; 15(3):261-269 1982

The efficacies of analog II (AII), a cyclopropyl derivative of stilbene, and of tamoxifen (TX) in producing the regression of established 7,12 dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumors and preventing the formation of new tumors as palpable masses were compared. Female Sprague-Dawley rats were used. No overt harmful or toxic effects were noted in any of the groups as a result of treatment with either TX or AII, nor could any evidence for such be determined by histological examination following complete necropsy and tissue sampling at the end of the 7-wk treatment period (TP). Both antiestrogens effectively decreased the percentage of animals with increased tumor vol and increased the percentage of animals with decreased tumor vol. AII significantly altered tumor growth (TG) between the third and fifth wk of TP and TX produced similar alterations in TG between the fifth and seventh wk. At the end of the TP, four of the eight AII-treated animals developed 9 new tumors while six of the seven control animals developed 12 new tumors and seven of the eight TX-treated animals developed 17 new tumors. Thus, AII protected 50% of the animals against new tumor development while only 12% of the TX-treated animals and 14% of the controls were similarily protected. Results indicate that AII is more effective than TX in protecting animals against development of new tumor masses during TP. (17 Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

66. DOES ENDOGENOUS CORTISOL PLAY A ROLE IN THE DEVELOPMENT OF CANCER?

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Med Hypotheses; 8(2):163-171 1982

Studies have shown an inverse relationship between physiological levels of cortisol and the number of lymphocytes in circulation, and the importance of lymphocytes ability to metabolize cortisol in the process of regulating the lymphocyte population. A blood factor called lymphocytic-cortisol-metabolism-enhancing factor (LCMEF) serves to maintain the homeostatic balance by enhancing cortisol metabolism by lymphocytes, thus acting as a counter-agent against the cortisol effects. The lack of LCMEF, preceding the development of malignancy, can induce lymphopenia, seen in cancer patients, and the depletion of cortisol-sensitive lymphocytes involved in the immune response against malignant cells. The cortisol effect would also explain the development of cancer in transplant patients who have undergone immunosuppression therapy. (43 Refs)

67. IMMUNOSUPPRESSION AND THE RHEUMATIC DISEASES.

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Ann Rheum Dis; 41(Suppl1):3-8 1982

When cytotoxic therapy for the rheumatic diseases was introduced, these diseases were regarded as autoimmune diseases. This concept is now recognized as an oversimplification. The autoimmunity and other immunologic abnormalities observed in rheumatoid arthritis and related diseases might represent the secondary effects of persistent antigen(s). Cytotoxic agents (at least, in the doses usually given to patients with rheumatic diseases) may enhance conventional immune responses. In patients with bone marrow depression and immunologic deficiencies secondary to connective tissue diseases, cytotoxic therapy commonly causes a paradoxical improvement of bone marrow function and host resistance to infection. If rheumatoid arthritis is in fact a primary immunoproliferative disease, the beneficial effects of cytotoxic agents may be related to their selective effects on proliferating cells, rather than their immunosuppressive effects (which could be irrelevant or even undesirable). Available evidence on the pharmacologic events of inflammation has called into question the belief that the beneficial effects of glucocorticoids are related to their effects on immune function. In fact, the latter effect might represent an undesirable side effect of steroids. The mechanisms of action of cytotoxic agents and steroids in rheumatoid arthritis and related diseases will not be clear until the pathogenesis of these diseases is understood. (15 Refs)

68. IMMUNOCHEMICAL STUDY OF ANDROGEN-BINDING BETA-GLOBULIN IN HEALTHY CONTROLS AND CANCER PATIENTS.

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Dept. Biological Chemistry, N. I. Pirogov Second Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 92(1):58-60 1982

Androgen-binding beta-globulin (ABBG) was assayed in blood sera and tissue extracts of healthy controls and cancer patients. Immunodiffusion and immunoelectrophoresis showed the presence of ABBG in extracts of the prostate and the sperm, but not in the blood sera, of the healthy controls. The ABBG was present in tumor tissue extracts of the patients with breast cancer, kidney cancer, stomach cancer, colonic cancer, brain cancer, or testicular cancer and in the blood sera of 50% of the cancer patients. Tests for cross reactions showed that the ABBG was not identical to antigens showing affinity to steroid hormones. (13 Refs) (In RUS)

GENERAL REVIEWS ON STEROID HORMONES

69. DIAGNOSTIC STRATEGIES IN DISORDERS OF FLUID, ELECTROLYTE AND ACID-BASE HOMEOSTASIS.

Narins RG, Jones ER, Stom MC, Rudnick MR, Bastl CP
Temple Univ. Health Sciences Center, Philadelphia, PA, 19140
Am J Med; 72(3):496-520 1982

Our understanding of the physiology and biochemistry of acid-base and fluid-electrolyte regulation has greatly expanded in recent yr. Key physiologic principles have emerged that now permit rational diagnosis and therapy of clinical disorders of serum electrolyte concentration. This paper describes diagnostic strategies based upon these principles. The etiology of the myriad factors in hyponatremia is best derived by first measuring serum tonicity and then assessing extracellular fluid volume. The hyper-, iso- and hypotonic hyponatremias are defined, and the hypotonic group is subclassified into hypo-, iso- and hypervolemic forms. The hypernatremias are best categorized by their state of volume expansion. Classification into the hypo-, hyper- and isovolemic hypernatremias simplifies their diagnosis. Metabolic acidoses are classified in terms of the anion gap. Clinical and chemical aspects of increased and normal anion gap acidoses are described. Metabolic alkaloses require a source of new bicarbonate and its retention by the kidney. The means by which new alkali is synthesized and urinary loss prevented serve to effectively classify the alkaloses. Hypokalemic syndromes are defined in terms of associated changes in body potassium. The potassium-depleted states are further subclassified by whether normotension or hypertension is associated. Hyperkalemia is produced by redistribution of cellular and extracellular potassium or by increased body potassium. Defects in the renin-angiotensin-aldosterone-distal renal tubule effector arm usually underlie hyperkalemic states, which are then classified in terms of this regulatory hormonal cascade. Classifications for disordered serum concentrations of calcium, magnesium, phosphorus and uric acid are presented. Hormonal, metabolic and renal regulatory factors form the basis for an organized approach to these disorders. (Author abstract) (68 Refs)

70. HORMONES IN CANCER THERAPY.

Rosenthal RC
1008 West Hazelwood Drive, Coll. Veterinary Medicine, Univ. Illinois, Urbana, IL, 61801
Vet Clin North Am [Small Anim Pract]; 12(1):67-77 1982

Use of hormones for cancer treatment in animals is reviewed. Adrenal corticosteroids, particularly prednisone, have been used to treat hemolymphatic neoplasia and mast cell tumors. Recommendations are made for induction combination chemotherapy for multicentric canine lymphosarcoma and single agent chemotherapy for disseminated or recurrent mast cell tumors. Avoidance of high-dose prednisone for tumors not known to be particularly susceptible to the effects of corticosteroids is suggested. Glucocorticoids are able to cross the blood-brain-barrier and may be useful in treating brain tumors. Theoretically, prednisolone should be used instead of prednisone. Sex hormones are used for treatment of tumors with a recognized hormonal dependence. Diethylstilbestrol (DES), estradiol cycloproprionate (ECP), and testosterone have been used for perianal gland adenomas, prostatic neoplasia, and mammary tumors. Tamoxifen is the drug of choice for antiestrogenic activity and will possibly be used when estrogen receptor analysis becomes more available in canine mammary tumors. Hormones can also be used as replacement therapy, suppressors of tumor growth and metastatic spread, or as adjuncts in management of paraneoplastic syndromes. (39 Refs)

71. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.

Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

Side effects of sex hormones and related compounds are reviewed. Hormonal replacement therapy is discussed with respect to conjugated estrogens, estrogen/progestogen combinations, estriol succinate, estradiol valerate, a combination of the two preceding drugs, intravaginally administered estrogens, and benefits vs risks. Treatment with sex hormones of breast and liver tumors, industrial exposure to steroid hormones used in oral contraceptives (OC), gall bladder disease, psychic changes, acute intermittent porphyria, prolactin secretion in cases of pituitary adenoma and in lactating women, injectable and implanted steroidal contraceptives, low-dose combination OC, progestogen-only OC, combination of estrogens with cyproterone acetate, hormonal contraceptives and vitamins, teratogenicity, antiestrogens, and antiandrogens are each discussed. (159 Refs)

72. CURRENT INFORMATION ON THE MECHANISM OF ACTION OF SYNTHETIC ESTROGENS.

Rochefort H
Unite d'Endocrinologie Cellulaire et Moleculaire, I.N.S.E.R.M. (U 148), 60 rue de Navacelles et UER de Medecine, 34100 Montpellier, France
Biochimie; 64(2):89-98 1982

Synthetic antiestrogens such as tamoxifen (Nolvadex) are currently used to treat postmenopausal breast cancer. Their mechanism of action is reviewed at the cellular and molecular level, through data of the literature and the current view of the author. Synthetic antiestrogens are mostly acting directly on breast cancer cells by interacting with the estrogen receptor (RE). They prevent estrogen action by competing with estrogens on the cytosol RE. The resulting complex is partially activated resulting in its nuclear localization and a partial and dissociated stimulation of the expression of estrogen responsive genes. The explanation of the antitumoral effect of these drugs is more controversial, since the regulation of cell proliferation is not only due to estrogens but also to other hormones and factors. The antiestrogens can therefore block cancer cell growth by inhibiting estrogen action, or by a RE mediated cytotoxic effect and/or by any other mechanism involving indirect effects, or binding to other proteins than the RE. (Author abstract) (45 Refs) (In FRE)

73. PARANEOPLASTIC ENDOCRINOPATHIES ASSOCIATED WITH NONRENAL GENITOURINARY TUMORS.

Altaffer LF
Dept. Urology, Naval Regional Medical Center, Camp Lejeune, NC
J Urol; 127(3):411-416 1982

The ectopic or inappropriate production of parathyroid hormone (PTH), catecholamines (CTA), serotonin (ST), human chorionic gonadotropin (HCGT), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), calcitonin, estrogens (ES), human placental factor (HPF), erythropoietin, insulin-like substances, and prostaglandins associated with various renal tumors is reviewed. Several case reports of apparent PTH secretion by urothelial tumors exist. In all of the cases resolution of the hypercalcemia followed definite treatment of the cancer. Diagnosis of pheochromocytoma is made by measuring elevated serum, urinary CTA and metabolites. Prognosis is generally good but long-term follow-up with urinary levels of CTA or the metabolites is recommended. Signs and symptoms of some carcinoid tumors are probably caused by excessive production of ST. The secretion of HCGT by testicular neoplasms is well known and the use of HCGT as a tumor marker is applied in practice. ACTH was identified in three cases of carcinoma of the prostate. In 1969, a case of carcinoma of the prostate with evidence of ectopic secretion of ADH by the neoplasm was reported. The secretion of a thyroid stimulating hormone-like substance has been reported in association with trophoblastic tumors in women and in two cases of testis tumors. The secretion of ES, androgens, pregnanediol, and luteinizing hormone, has been associated with Leydig cell tumors, gonadal stromal tumors, and gonadoblastomas. The identification of HPF in the syncytiotrophoblastic cells in malignant teratoma of the testis was reported in 1966. Hypoglycemia has been shown to be associated with a variety of extrapancreatic tumors. Hormonally active tumors frequently demonstrate undifferentiated or anaplastic histologic patterns and, in general, patients with hormonally active tumors appear to have a poor prognosis. (83 Refs)

74. SYSTEMIC THERAPY OF METASTATIC BREAST CANCER: A REVIEW OF THE CURRENT TRENDS.

Legha SS, Blumenschein GR
M. D. Anderson Hosp., 6723 Bertner Ave., Houston, TX, 77030
Oncology; 39(3):140-145 1982

This paper reviews the different options of systemic therapy available for the management of patients with metastatic breast cancer. Endocrine therapy with tamoxifen, aminoglutethimide, progestins or androgens are useful for approx one half of the patients either before or after chemotherapy. Combination chemotherapy is effective in approx 75% of the patients and offers the best palliation for the majority of the patients. Adriamycin-containing regimens have resulted in slightly superior results than combination regimens which exclude adriamycin from first line chemotherapy. Secondary chemotherapy is useful only in 25-30% of the patients and responses usually do not last longer than 4-6 mo. With carefully planned and properly sequenced treatment approaches, patients with metastatic breast cancer have a median survival of 2 yr and a 5-yr survival of 10-15%. (Author abstract) (25 Refs)

75. THE MENOPAUSE: BENEFITS AND RISKS OF ESTROGEN-PROGESTOGEN REPLACEMENT THERAPY.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Fertil Steril; 37(4):457-474 1982

The benefits of cyclic estrogen-progestogen administration for the relief of vasomotor symptoms, urogenital atrophy, psychosomatic complaints, osteoporosis, and possibly cardiovascular risks are reviewed. Risks of endometrial cancer and hyperplasia, breast cancer, thromboembolic phenomena, and gallbladder disease are discussed. The benefits of appropriate postmenopausal estrogen therapy seem to outweigh the risks for many women, although not all need such therapy; some with significant levels of endogenous estrogen may need progestogens to reduce the risk of endometrial cancer. (90 Refs)

OTHER RELATED STUDIES

76. POSTMENOPAUSAL VAGINAL CYTOHORMONAL PATTERN IN 597 HEALTHY WOMEN AND 301 PATIENTS WITH GENITAL CANCER.

Efstratiades M, Tamvakopoulou E, Papatheodorou B, Batrinos M
M.I.A.C., 4 Dimocritou St., Athens 134, Greece
Acta Cytol (Baltimore); 26(2):126-130 1982

Cytohormonal evaluation was made on vaginal smears of three groups of women, all over 50 yr of age and menopausal for at least 1 yr. The first group consisted of 597 control healthy women, and the second and the third groups consisted of 134 patients with squamous cervical cancer and 167 patients with endometrial adenocarcinoma, respectively. It was found that 4% of the 597 healthy women had vaginal smears with an unequivocal estrogenic effect as compared with a 6% incidence in patients with squamous carcinoma of the cervix and a 12% incidence in patients with endometrial adenocarcinoma. It is concluded that increased estrogenic activity in a woman more than 1 yr after menopause should lead to a thorough clinical investigation to exclude an asymptomatic carcinoma of the cervix or endometrium. (Author abstract) (41 Refs)

77. THERAPEUTIC EFFECT ON GALACTORRHEA AND STERILITY IN PROLACTIN-SECRETING PITUITARY ADENOMAS.

Sato O, Tanabe S, Tsuchita H, Nakagawa T, Inoue Y, Daibo M, Uede T, Hotta H
Dept. Neurosurgery, Sapporo Medical Coll., Sapporo 060, Japan
Neurol Med Chir (Tokyo); 21(11):1123-1133 1981

The authors investigated factors responsible for cessation of galactorrhea or restoration of ovulation in 30 women with PRL-secreting pituitary adenomas after surgery with or without bromocriptine. All the patients complained of sterility and 25 patients had galactorrhea. Microsurgical removal of adenomas was performed in all the patients and 15 patients received oral bromocriptine after surgery on account of sustained elevated serum PRL levels. Galactorrhea ceased in 19 out of 25 patients (76.0%) after the treatment. Preoperative serum PRL levels, age of patients at surgery, duration of galactorrhea, history of nursing, severity of galactorrhea and serum estradiol or progesterone levels had no correlation with cessation of galactorrhea. Ovulation was restored in 18 of 30 patients (60.0%) after the treatment and pregnancy was established in 12 patients. The PRL levels where ovulation was restored ranged from 3 to 57 ng/ml. The normal PRL levels did not inevitably ensure restoration of ovulation. There was no difference in the frequency of restoration of ovulation after the treatment between patients with preoperative PRL levels below 200 ng/ml after surgery. There was a prevalence in the frequency of restoration in amenorrhea Grade I, preoperative duration of sterility of less than 5 yr, microadenomas, a longer postoperative interval normal serum basal LH levels and peak LH levels in response to LH-RH and the presence of positive feedback control to surge LH in response to estrogen. Age of the patients at surgery, elevated dopamine activity in the hypothalamus and serum estradiol or progesterone levels were not correlated with restoration of ovulation. (36 Refs) (In JPN)

78. MONOCLONAL ANTIBODIES IN CLINICAL DIAGNOSIS: REAGENTS FOR DETECTING HORMONES AND IMMUNOGLOBULINS.

Wang L, Hexter CS, Inbar M
Dept. Cell Biology, Miles-Yeda, Kiryat Weizmann, Rehovot, Israel
Protides Biol Fluid Proc Colloq; 29:817-822 1982

Monoclonal antibodies to thyroxine, triiodothyronine, human chorionic gonadotropin, and human gammaglobulin were obtained from hybrid cells derived from fusion of spleen cells of immunized BALB/c mice and P3-NSI/1Ag4 mouse myeloma cells. Advantages and disadvantages of the use of these monoclonal antibodies in clinical immunoassays are discussed. (7 Refs)

79. MASSIVE HYPERPLASIA OF TESTICULAR ADRENAL RESTS IN A PATIENT WITH NELSON'S SYNDROME.

Johnson RE, Scheithauer B
Section Publications, Mayo Clinic, Rochester, MN, 55905
Am J Clin Pathol; 77(4):501-507 1982

The case of a 23-yr-old man with Nelson's syndrome is presented. He had undergone bilateral adrenalectomy at age 15 yr for Cushing's syndrome. Postoperatively, his cushingoid features resolved; however, 13 mo later, he became hyperpigmented and showed radiographic evidence of sellar enlargement and midline expansion of the sellar floor. In 1972, he received radiation therapy to the pituitary gland. He underwent transsphenoidal hypophysectomy in 1974 and 1975 for recurrent pituitary adenoma, and recurrent Cushing's syndrome developed concomitantly with bilateral firm testicular masses in 1978. External scanning with NP-59 localized steroid production to the testes, and bilateral orchiectomy was performed. Immunohistochemical studies of the pituitary tumor confirmed the presence of adrenocorticotropic hormone, and morphologic and ultrastructural examinations of the testes supported the adrenal nature of the testicular tumors. (Author abstract) (8 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STEROID HORMONE SYNTHESIS AND METABOLISM

1. ABNORMAL OXIDATIVE METABOLISM OF ESTRADIOL IN WOMEN WITH BREAST CANCER.

Schneider J, Kinne D, Fracchia A, Pierce V, Anderson KE, Bradlow HL, Fishman J
(c/o Fishman) Rockefeller Univ., 1230 York Ave., New York, NY, 10021
Proc Natl Acad Sci USA; 79(9):3047-3051 1982

The three dominant oxidative biotransformations of estradiol were examined in 10 normal women and 33 females with breast cancer by using a recently devised radiometric method. Estradiol tracers, labeled with 3H specifically in the 17alpha, C-2, or 16alpha position, were used to measure both the rate and extent of 17beta-ol oxidation (the initial metabolic step) and the subsequent 2-and 16alpha-oxidative reactions. The mean +- SEM values for the extent of estradiol metabolism at these three specific sites were 76.9 +-5.3%, 31.1 +-4.0%, and 9.3 +-0.8%, respectively, in normal subjects. Corresponding data in patients with breast cancer - ie, 73.0 +-4.2%, 32.7 +-2.7%, and 14.9 +-1.5% - revealed a significantly greater extent of 16alpha-hydroxylation in the latter population. Because of the 16alpha-hydroxylated compounds (including estriol) are themselves potent estrogens, these changes may have important hyperestrogenic consequences that could have a bearing on the etiology of the disease. (Author abstract) (36 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

2. PROSTAGLANDINS AND BENIGN MASTOPATHIES.

Rolland PH, Martin PM, Bourry M, Serment H
Laboratoires des recepteurs hormonaux de Cancerologie Experimentale, Faculte de Medecine de Marseille (Secteur Nord), F 13326 Marseille Cedex 3, France
J Gynecol Obstet Biol Reprod (Paris); 10(3):197-201 1981

Levels of plasma estrogen (E), progesterone (P), and prostaglandin synthetase (PS) activity were measured in 22 women (23-28 yr old) who had symptoms of benign mastopathy or mastodynia during all or part of their menstrual cycle. Thermographic examinations were performed. In general, E and P levels were decreased in the patients as compared with normal subjects. Prostaglandin E2 (PGE2) levels were increased during both phases of the menstrual cycle among patients. In four benign lesions examined, levels of PS activity were variable. Patients with low estrogen levels showed a pronounced thermographic response to treatment with prostaglandin inhibitors, while patients with high relative estrogen levels showed no such response. The relationships between E, P, and PGE2 levels and risk of breast cancer are discussed. (19 Refs) (In FRE)

3. ENDOCRINOLOGICAL STUDIES ON PROSTATIC CARCINOMA. 1. PLASMA HORMONE PROFILES IN PATIENTS WITH PROSTATIC CARCINOMA.

Morioka M
Dept. Urology, Okayama Univ. Medical Sch., Okayama, Japan
Nippon Hinyokika Gakkai Zasshi; 72(8):953-966 1981

Levels of plasma testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin were determined in 47 patients (49-87 yr old) with prostatic carcinoma before and during antiandrogen therapy. Hormonal dynamics were not related to the course of the disease. Rather, the levels of the hormones were primarily a result of pharmacological effects of the drugs. However, pretreatment levels of DHEA-S were significantly lower in the 26 Stage IV carcinoma patients than in the Stage I, II, and III patients; this was thought to be related to aging factors and the general condition of the patients. Synthetic progestogens (50-100 mg/day, 3-79 mo) and diethylstilbestrol diphosphate (DES-DP; 300 mg/day, 3-18 mo) decreased T-cell production and levels of DHEA and DHEA-S while estramustine phosphate (EP; 560-840 mg/day, 4-22 mo) inhibited T-cell production but had no inhibitory effect on DHEA or DHEA-S. The EP more strongly inhibited FSH levels than synthetic progestogens. Based on ACTH-Z and single dose metyrapone tests in patients undergoing treatment, DES-DP was thought to have inhibitory effects on DHEA and DHEA-S due to mild inhibition of ACTH and C17-C20 lyase activity in the adrenal glands. On the other hand, the EP was thought to have no inhibitory effect on steroid production in the adrenal glands. No relationship was found between adrenal androgen levels and the reactivation of prostatic carcinoma in patients who relapsed. (46 Refs) (In JPN)

4. HYPOGONADISM IN MALE PATIENTS WITH METASTATIC CANCER PRIOR TO CHEMOTHERAPY.

Chlebowski RT, Heber D
Div. Medical Oncology, Harbor-Univ. California Los Angeles Medical Center, 1000 West Carson St., Torrance, CA, 90509
Cancer Res; 42(6):2495-2498 1982

Gonadal hormonal function was assessed in 44 adult males with disseminated cancer prior to chemotherapeutic treatment of their cancer by determination of plasma testosterone, free testosterone, and luteinizing hormone (LH) levels. Low values for both testosterone (43% decreased) and free testosterone (66% decreased) were seen in this largely malnourished cancer population, in which 82% of patients were less than 90% of ideal body weight. Four patterns of serum testosterone and LH were seen: (a) normal testosterone and normal LH (12 cases); (b) normal testosterone and high LH (13 cases), consistent with early primary hypogonadism; (c) low testosterone and high LH (10 cases), consistent with frank primary hypogonadism; (d) low testosterone and normal or low LH (9 cases), consistent with secondary hypogonadism. Significantly decreased ideal body weight was found in the group with low testosterone and low or normal LH level. We conclude that decreased gonadal hormone secretion is frequently seen in adult males with advanced cancer and malnutrition even prior to chemotherapy treatment. (Author abstract) (34 Refs)

5. THE EFFECT OF OVARIECTOMY ON EXCRETION OF URINARY STEROIDS AND TUMOR GROWTH IN RATS BEARING 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED MAMMARY CANCER.

Nakamura Y, Kodama M, Kodama T
Dept. Surgery, Inst. Balneotherapeutics, Kyushu Univ., 4546 Tsurumihara, Beppu 874, Japan
Gan; 73(2):234-238 1982

The relation between the excretion of urinary steroids and the therapeutic effect of ovariectomy on tumors was investigated in female Sprague-Dawley rats bearing 7,12-dimethylbenz[a]anthracene-induced mammary cancer. Ovariectomy significantly reduced the excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), but hardly affected that of urinary corticosteroid, 17-deoxy-corticosteroid (17-DOCS). The responsiveness of tumors to ovariectomy was positively correlated with both pre-operative 11-DOOS and pre-operative ratio of 11-DOOS to 17-DOCS, and negatively correlated with pre-operative 17-DOCS. The extent of tumor regression after ovariectomy was associated with the decrease of urinary androgen. A similar correlation was observed between the decrease in the ratio 11-DOOS/17-DOCS and tumor suppression during cyclophosphamide treatment (medical ovariectomy). These results indicated that the tumor response to ovariectomy was related to a shift of the endogenous hormone balance from a relative dominance of androgen to relative dominance of corticosteroid. The significance of the hormonal findings is discussed in the light of the steroid metabolism in human breast cancer. (Author abstract) (16 Refs)

6. PLASMA ANDROGEN LEVELS AFTER SUBCAPSULAR ORCHIECTOMY OR ESTROGEN TREATMENT FOR PROSTATIC CARCINOMA.

Vermeulen A, Schelfhout W, De Sy W
Dept. Endocrinology and Metabolism, Univ. Ghent, Ghent, Belgium
Prostate; 3(2):115-121 1982

Following bilateral subcapsular orchiectomy for advanced prostatic carcinoma (APC) in 40 patients, the plasma levels of testosterone were within the range found in postmenopausal women and remained at these levels for one year. Plasma androstenedione (A) levels were 75-80% of the levels in normal men and also remained constant over one yr. Dehydroepiandrosterone (D) and dehydroepiandrosterone sulfate (DS) levels remained at essentially the same as those of normal men. In another group of 35 patients with APC treated only with polyestradiol phosphate (80 mg/mo im), levels of D after several months were the same as controls. The levels of A were about 70% of controls while levels of DS were significantly lower. The results indicate that during the year following subcapsular orchiectomy there is no reactivation of any remaining Leydig cells and no compensatory adrenal androgen secretion, nor is there an increased adrenal androgen secretion during estrogen treatment. There was no evidence in either group of patients for increased androgen levels at the time of recurrence of the carcinoma. (21 Refs)

7. A DIRECT RADIOIMMUNOASSAY OF PLASMA ALDOSTERONE IN NORMAL SUBJECTS AND PATIENTS WITH HYPERTENSION OR RENAL DISEASE USING 125I-LABELED LIGAND (ALDOCTK-125 KIT).

Kawasaki T, Nakamuta S, Omae T
Second Dept. Internal Medicine, Kyushu Univ. Faculty Medicine, Fukuoka 812, Japan
Fukuoka Igaku Zasshi; 72(11):633-638 1981

Plasma aldosterone concentrations (PAC) were measured in normal subjects (25 males and 17 females) and in patients with essential hypertension (51), primary aldosteronism (PA: 10), renovascular hypertension (10), pheochromocytoma (PC:4), chronic glomerulonephritis (18), or malignant hypertension (10). The PAC was 14.7 +-4.1 ng/deciliter in the PC patients; it did not increase significantly in the PA and PC patients administered low-salt (NaCl, 2g/day) diets for 4 days. Within 4 wk after unilateral adrenalectomy, the PAC in the PA patients was almost the same as that in the PC patients on a control diet (NaCl, 10g/day), and the PAC was significantly increased by the low-salt diet. (20 Refs) (In JPN)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

8. USE OF ESTRADIOL-CONTAINING LIPOSOMES FOR THE SELECTIVE TRANSPORT OF SUBSTANCES INTO THE CELLS OF ESTROGEN-DEPENDENT TISSUES AND TUMORS.

Morozova TM, Budker VG, Gutkina NI, Moiseeva GI, Salganik RI
Inst. Cytology and Genetics, Novosibirsk, USSR
Eksp Onkol; 4(2):47-50 1982

An attempt was made to incorporate estradiol (E) into liposome membrane and thus to enhance the selective transport of E into the estrogen-dependent target tissues. Ovariectomized DD mice bearing mammary gland carcinoma were inoculated iv with free E or with E-containing liposomes. Incorporated E showed more rapid binding to the uterus and liver than the free E. E-containing liposomes showed more intensive incorporation into uterus tissue than E-free liposomes. (15 Refs) (In RUS)

9. STEROID HORMONE RECEPTOR OF ACUTE LEUKEMIC CELLS IN CHILDHOOD, WITH SPECIAL REFERENCE TO RECEPTOR LEVEL AND CHEMOTHERAPY.

Shimizu S, Asao T, Ido M, Kamiya H, Sakurai M
Dept. Pediatrics, Sch. Medicine, Mie Univ., Tsu, Mie Prefecture, Japan
Rinsho Ketsueki; 22(11):1714-1719 1981

Glucocorticoid (GC) receptor level in acute leukemic blast cells in childhood was measured in 40 cases of acute lymphoblastic leukemia (ALL) and 10 of acute myelogenous leukemia (AML). Although the level of GC receptor in leukemic cells of ALL was variable, its mean receptor level was clearly higher than that in AML or in the normal lymphocytes. The prognosis of leukemia apparently correlated with the GC level. The GC receptor level was lower in relapsed leukemic cells compared to that in pretreated leukemic cells. Drugs other than GC should be used to treat patients with a low level of GC receptors. (15 Refs) (In JPN)

10. ESTROGEN RECEPTORS AND CLINICAL CORRELATIONS WITH HUMAN PROSTATIC DISEASE.

Pontes JE, Karr JP, Kirdani RY, Murphy GP, Sandberg AA
Dept. Urologic Oncology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Urology; 19(4):399-403 1982

Measurement of estrogen binding in human prostate using high-pressure liquid chromatography (HPLC) revealed the presence of cytosolic estrogen receptors (ER) both in benign prostatic hyperplasia (BPH) and adenocarcinoma. Receptor concentrations correlated with several histopathologic features in the specimens analyzed. Estrogen receptor levels generally were higher in BPH than in cancer specimens although there was a subgroup of patients with poorly differentiated carcinoma with levels higher than those of BPH. HPLC can be used for measuring ER in 50 ul of cytosol, and thus needle biopsy specimens will be analyzed routinely for ER with this micromethod. (Author abstract) (24 Refs)

11. DOES PROGESTERONE RECEPTOR IN HUMAN BREAST CANCER REFLECT THE MAST-CELL CONTENT OF THE TUMOUR TISSUE?

Thoresen S, Thorsen T, Hartveit F

Norwegian Cancer Society, Univ. Bergen, Bergen, Norway

Br J Cancer; 45(4):618-620 1982

Material from surgical specimens of patients (33-91 yr old) with infiltrating breast carcinomas treated by modified radical mastectomy was analyzed to determine whether progesterone receptor (RP) content reflects the mast-cell content. All PR negative (RP-) estrogen receptor negative (RE-) cases (17), RP-RE+ cases (18), and the first 29 RP+RE+ cases were examined. The mean values for the mast-cell count were related to the receptor profile of the tumors as judged from cytosol assay. The profile RP+RE- was not included since there were only three such cases. When the range and distribution of the mast-cell count was determined, great scatter was observed in all groups. A line dividing the material at 40 mast cells/20 high-power fields divided the RP-RE+ group almost in half, while only one value was over 40 in each of the other groups. In the 29 tumors with the common profile RP+RE-, the mean mast-cell count in 20 high-power fields was 13 +-14; that in the RP-RE+ group of 17 tumors was similar: 8 +-16. The mean mast-cell count was significantly higher in the 18 tumors with the profile RP-RE+. No relationship was found between the exact RP values and the mast-cell counts. Tumor mast cell content should be considered before a negative RP report is accepted. (15 Refs)

12. EFFECT OF ADRENAL MANIPULATION ON GLUCOCORTICOID RECEPTORS IN MM1 HAMSTER MELANOMA.

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(c/o Beattie) Div. Surgical Oncology, Univ. Illinois Medical Center, 840 S. Wood St., Chicago, IL, 60612

Cancer Res; 42(6):2242-2246 1982

Cytosol glucocorticoid receptor of hamster Malignant Melanoma Number 1 (MM1) was characterized by dextran-coated charcoal and sucrose gradient assays. MM1 contains a specific, saturable, high-affinity (Kd 2.5 nM; 73.3 fmol/mg cytosol protein) receptor for glucocorticoid. The receptor sedimented at 7 to 8S in low-salt buffer and 5.5S in 0.4 M KCl and was sensitive to proteolysis by trypsin. Glucocorticoid receptor was inactivated by 40% $(NH_4)_2SO_4$. Addition of 20 nM molybdate to the homogenizing buffer prevented inactivation. Adrenalectomy increased MM1 receptor content without altering affinity. Chronic exposure of intact or adrenalectomized hamsters to gluco- and high-dose mineralocorticoid significantly decreased the amount of unbound glucocorticoid receptors available for binding. Exposure of intact hamsters to high doses of mineralocorticoid also decreased apparent receptor affinity. These results suggest that hamster MM1 contains a high-affinity cytosol receptor for glucocorticoids similar to that of other glucocorticoid-responsive tissues, which may mediate the action of adrenal steroids on tumor behavior. (Author abstract) (24 Refs)

13. BIOLOGICAL CHARACTERISTICS AND ESTROGEN AND PROGESTERONE RECEPTORS IN MAMMARY CARCINOMA INDUCED IN MALE SPRAGUE-DAWLEY RATS BY A SERIES OF INTRAGASTRIC INTUBATIONS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Yoshida H, Yoshida A, Fukunishi R, Sato B, Okamoto S, Matsumoto K

Inst. Comparative Medicine and Animal Experimentation, Sch. Medicine, Ehime Univ., Shitsukawa, Shigenobu-cho, Onsen-gun, Ehime, 791-02, Japan

Cancer Res; 42(6):2434-2439 1982

Biological characteristics and estrogen (ER) and progesterone (PR) receptors were studied in male mammary carcinomas induced by 7,12-dimethylbenz(a)anthracene (DMBA) in male inbred Sprague-Dawley rats (MM). DMBA-induced carcinomas in females (MF) were used as controls. In 26 of 44 female rats given 20 mg DMBA once by gastric intubation at 50 days of age, MF with microscopic characteristics of cystic papillary adenocarcinoma developed 124 +-49 (S.D.) days after challenge. In all of the 42 male rats given 10 mg DMBA at 14-day intervals for 14 wk starting from 28 days of age, MM with microscopic characteristics of medullary adenocarcinoma developed 106 +-21 days after the first intubation of DMBA. The growth of primary MM was unaffected by orchiectomy or estrogen. Eighty to 100% of the MM transplanted in the four groups could grow in intact female rats, ovariectomized female rats, intact male rats, and castrated male rats, while the transplanted MF could grow only in intact female rats. The histology of MM was unchanged in primary and transplanted tumors under various hormonal conditions. ER were present in almost all of the hormone-independent primary and transplanted MM, although the levels for cytosol ER in MM were significantly lower than those in MF. Injection of 10 ug 17beta-estradiol induced marked synthesis of PR in primary and transplanted MM, even 24 and 48 hr after the 17beta-estradiol injection. These findings show that MM are hormone independent but, like hormone-dependent female tumors, contain ER and estrogen-dependent PR. (Author abstract) (24 Refs)

14. RETINOIC ACID BINDING PROTEINS AND STEROID RECEPTOR LEVELS IN HUMAN BREAST CANCER.

Mehta RG, Kute TE, Hopkins M, Moon RC

Life Sciences Div., ITT Res. Inst., 10 West 35th St., Chicago, IL, 60616

Eur J Cancer Clin Oncol; 18(3):221-226 1982

Samples of 31 human breast cancer tissues were examined for the presence or absence of cytosolic retinoic acid binding proteins (cRABP), estrogen receptors (ER) and progesterone receptors (PR). cRABP were detected as specifically sedimenting 2S components on sucrose density gradients. Specific binding under the 2S region for cRABP and under the 8S region for ER and PR were determined. The levels of cRABP ranged from less than 1 pmol to 14 pmol per mg of cytosol protein. Tumors containing less than 3 pmol cRABP were designated as low cRABP; tissues were considered ER- and PR- when the receptor levels were less than 10 fmol/mg protein. Approx 60% of primary and metastatic tumors examined contained high cRABP. Tumors with well differentiated histopathology exhibited increased levels of cRABP. There was no significant correlation between the presence or absence of steroid receptors and cRABP in human mammary tumors. (Author abstract) (25 Refs)

15. LACK OF CORRELATION OF A HISTOCHEMICAL METHOD FOR ESTROGEN RECEPTOR ANALYSIS WITH THE BIOCHEMICAL ASSAY RESULTS.

Panko WB, Mattioli CA, Wheeler TM
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer; 49(10):2148-2152 1982

Forty-nine specimens of carcinoma of the breast were analyzed for estrogen receptor content using the sucrose gradient method and a histochemical method using a conjugate of estradiol (6-BSA-Fluor-CMO-17beta-estradiol). The specimens analyzed by the histochemical method were graded for fluorescent intensity, percentage of cells fluorescing, and cellularity. Only 53.1% (26/49) of the specimens were classified into the same three categories (positive, negative and ambiguous) as classified by the biochemical assay. If the negative and ambiguous categories were combined, the degree of correspondence rose to only 63.3% (31/49). Because the classification scheme was arbitrary and because the results of the biochemical assay might be correlated with one or more factors, univariate and multivariate analyses were used to examine the data for any underlying relationships. Only the age of the patient was significantly correlated with the results of the biochemical assay. Importantly, neither the percentage of cells fluorescing nor the fluorescent intensity was correlated with the results of the biochemical assay. Terms to account for various interactions of parameters did not enhance the association with the biochemical results. While this histochemical assay may eventually prove to be effective in selecting patients for endocrine therapy, it does not seem to be a substitute for the standard biochemical assay for estrogen receptors presently used. (Author abstract) (11 Refs)

16. THE DETECTION OF ESTROGEN RECEPTORS IN GYNECOLOGIC TUMORS USING IMMUNOPEROXIDASE AND THE DEXTRAN-COATED CHARCOAL ASSAY.

Farley AL, O'Brien T, Moyer D, Taylor CR
(c/o Taylor) Dept. Pathology, Univ. Southern California, 2025 Zonal Ave., Los Angeles, CA, 90033
Cancer; 49(10):2153-2160 1982

The dextran-coated charcoal receptor assay for demonstrating functional estrogen and progesterone receptors was used to evaluate the receptor content of gynecological tumors. An immunocytochemical method, the immunoperoxidase antiperoxidase method, that may detect estrogen receptors, was also employed on the same specimens utilizing sections from formalin-fixed paraffin embedded blocks. The results by the two methods were compared and were correlated with the state of differentiation of the tumors. According to the dextran-coated charcoal method, two cases of well differentiated endometrial adenocarcinoma were strongly positive for both estradiol and progesterone receptors, and three moderately differentiated cases contained lesser amounts of both types of receptors. Six cases of undifferentiated adenocarcinoma ranged from no detectable receptors to very high values, while of five cases of squamous cell carcinoma of the cervix, only two were positive for estradiol receptors by the dextran-coated charcoal method. Staining of tissue sections from these same cases using the immunoperoxidase method, demonstrated a positive correlation to the dextran-coated charcoal assay for estrogen receptors. The Dextran-coated charcoal method is presently being used clinically as a screening measure for statistical probability of a patient's response to hormone therapy. The degree of positive correlation shown here suggests that use of the immunoperoxidase method may have further potential for diagnostic and clinical use, and merits further investigation. (Author abstract) (25 Refs)

17. TAMOXIFEN-INDUCED FLUORESCENCE AS HORMONE DEPENDENCE MARKER: A CYTOLOGICAL STUDY ON BIOPSY SPECIMENS OF MALIGNANT BREAST TUMORS FROM TREATED WOMEN.

Mouriquand J, Mouriquand C, Sage JC, Saez S, Jacrot M, Gabelle Ph
Laboratorie d'Histologie, Faculte de Medecine de Grenoble, 38700 La Tronche, France
C R Acad Sci [III] (Paris); 293(15):801-806 1981

Tamoxifen-induced fluorescence in tumor cells obtained by biopsy and/or surgery from women treated with Tamoxifen for 8-60 days for breast carcinoma. Carcinoma cells from untreated women served as controls. Estradiol and progesterone receptors were found in 12/16 and 3/16 control tumors, respectively. Cellular fluorescence was not observed in the tumors of the untreated patients. Progesterone receptors were found in 10/15 tumors from Tamoxifen-treated patients. Estradiol receptors were found to be absent. Strongly positive cellular fluorescence was found in 8/10 tumor containing progesterone receptors from the Tamoxifen-treated patients. The findings indicate a very strong correlation between the presence of progesterone receptors and cellular fluorescence after Tamoxifen treatment. Determination of cellular fluorescence seems to be a suitable method for predicting response to hormone therapy in breast cancer patients. (23 Refs) (In FRE)

18. MOLECULAR MECHANISMS OF ACTIVITY OF HORMONE-LINKED CYTOSTATICS.

Belousova AK, Boguslavskaia OA, Bergol'ts VV, Shkodinskaia EN, Kurdiumova KN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):41-46 1982

The effect of steroid carrier on the alkylating activity of distrone (ester of chlorophenacyl and androgen) and phenthyrine (a derivative of thyronine) was studied in mice bearing ascites sarcoma 37. Analysis of single-stranded breaks and cross-links in DNA molecule showed that the alkylating activity of distrone was approx 10x lower than that of chlorphenacyl. Distrone caused marked and prolonged inhibition of 3H-androgen binding with chromatin from cells of the ventral prostate, while chlorophenacyl did not affect the nuclear acceptor sites. Phenthyrine caused a 40-70% inhibition of labeled triiodothyronine binding with cellular receptors. (30 Refs) (In RUS)

19. ESTROGEN-INSENSITIVE PROGESTERONE RECEPTORS IN A HUMAN BREAST CANCER CELL LINE: CHARACTERIZATION OF RECEPTORS AND OF A LIGAND EXCHANGE ASSAY.

Mockus MB, Lessey BA, Bower MA, Horwitz KB
(c/o Horwitz) Dept. Medicine and Biochemistry, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Endocrinology; 110(5):1564-1571 1982

In modified culture conditions, T47D human breast cancer cells synthesize extraordinary amounts of progesterone receptors (PgR), but, unlike other progesterone target cells, the PgR are entirely independent of estrogen controls. In the present studies we characterize some physicochemical properties of the PgR in T47D cells. We also describe an exchange assay for cytoplasmic and nuclear forms of the receptors which has enabled us to demonstrate that after progesterone treatment, translocation is stoichiometric. Despite the anomalous regulation of PgR levels, these receptors are typical of steroid receptors; they sediment at 7-8S on sucrose density gradients, they bind ligands with high affinity (Kd approx 4 nM for R5020; Kd approx 2 nM for progesterone), they bind only progestins specifically, and they are thermolabile (t1/2 at 37 c is approx 15 min). Receptor levels range from 15-40 pmol/mg DNA, or more than 300,000 sites/cell. The ability of ligands to dissociate from and rebind to the receptors was measured and used in an exchange assay for nuclear PgR. The synthetic progestin R5020 dissociates readily from receptors (t1/2 approx 3 hr at 0 C and 1.5 hr at 10 C), and the dissociation of progesterone is even faster (t1/2 approx 30 min at 0 C). To quantify steroid exchange, receptor levels were measured in mixtures of hormone-filled and unfilled cytosols. These studies assess ligand dissociation and subsequent ligand rebinding. At 0 C for 4-18 hr or at 10 C for 4 hr, unlabeled progesterone dissociates from receptors, and R5020 rebinds all sites, resulting in 100% exchange. In contrast, despite the use of a variety of incubation times and temperatures, no more than 50% of receptors previously filled with R5020 can exchange for [3H]R5020. The progesterone to [H3]R5020 exchange assay was used to measure salt-extracted nuclear progesterone receptors. In cells treated for 5 min with 0.1 uM progesterone, all depleted cytoplasmic sites were quantitatively recovered from nuclei. These cells provide a new model system to study the molecular biology of human PgR. (Author abstract) (37 Refs)

20. A STUDY OF CYTOPLASMIC OESTROGEN RECEPTORS IN PATIENTS WITH BREAST CANCER IN A DISTRICT GENERAL HOSPITAL.

Spencer GR, Prothero DL, Dawkins PD, Akehurst AC, Turner DR
(c/o Akehurst) Musgrove Park Hosp., Taunton, England
Br J Surg; 69(4):191-192 1982

The tumors of 61 patients suffering from primary adenocarcinoma of the breast were assayed for estrogen receptors (ER), using the dextran-coated charcoal method. A statistically significant relationship (p less than 0.05) was found to exist between ER status and the histological grade of the tumor. No relationship was found between ER status and either tumor size or the pathological state of the axillary lymph nodes. It is concluded that it is a practical proposition to establish an ER assay service in a district general hospital, with subsequent benefits for the individual patient. (Author abstract) (13 Refs)

21. STEROID HORMONE RECEPTORS AND SEX CHROMATIN FREQUENCY IN BREAST CANCER.

Smethurst M, Bishun NP, Fernandez D, Allen J, Burn JI, Alaghband-Zadeh J, Williams DC
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 OTL, England
J Endocrinol Invest; 4(4):455-457 1981

Seventeen primary breast tumors were divided into three groups according to the frequency of sex chromatin and subdivided according to the presence or absence of steroid receptors. Of the cytosol estrogen receptor positive tumors, only 3/15 showed a sex chromatin frequency of less than 10%. Of the tumors with frequencies of 11-20% or greater than 20%, 7/7 had estrogen and progesterone receptors, 6/7 had cytosol and nuclear estrogen receptors, and 6/7 had all three receptors. A possible association between the presence of steroid hormone receptors and sex chromatin frequencies of greater than 20% is suggested. (12 Refs)

22. 16ALPHA-[77BR]BROMO-11BETA-METHOXYESTRADIOL-17BETA: A GAMMA-EMITTING ESTROGEN IMAGING AGENT WITH HIGH UPTAKE AND RETENTION BY TARGET ORGANS.

Katzenellenbogen JA, McElvany KD, Senderoff SG, Carlson KE, Landvatter SW, Welch MJ, Los Alamos Medical Radioisotope Group
Sch. Chemical Sciences, Univ. Illinois, 1209 W. California St., Urbana, IL, 61801
J Nucl Med; 23(5):411-419 1982

The compound 16alpha-[77Br]bromo-11beta-methoxyestradiol-17beta [MBE(Br-77)], with high affinity for the estrogen receptor and with low nonspecific binding, has been prepared with an effective specific activity of 770-1,450 Ci per mmole at the time of synthesis. In immature female rats, this compound is taken up selectively by the uterus and is retained for prolonged periods. This is presumably due to the binding of this compound to the estrogen receptor, as uterine uptake is blocked selectively by coadministration of an excess of unlabeled estradiol, and administration of a chase dose of unlabeled estradiol results in a rapid decrease in activity in the uterus. In double-label experiments with 16alpha[125I]estradiol and MBE(Br-77), the two compounds showed equally selective uterine uptake at 1 hr, but the bromine-labeled compound became increasingly more selective at 3 and 6 hr. MBE(Br-77) may prove to be a more favorable agent for imaging human breast tumors than our previously described compound, 16alpha-[77Br]bromoestradiol-17beta. (Author abstract) (26 Refs)

23. IN VIVO COMPARISON OF 16ALPHA[77BR]BROMOESTRADIOL-17BETA AND 16ALPHA-[125I]IODOESTRADIOL-17BETA.

McElvany KD, Carlson KE, Welch MJ, Senderoff SG, Katzenellenbogen JA, Los Alamos Medical Radioisotope Group
Mallinckrodt Inst. Radiology, Washington Univ. Sch. Medicine, 510 South Kingshighway, St. Louis, MO, 63110
J Nucl Med; 23(5):420-424 1982

An in vivo comparison of two estrogen-receptor-binding radiopharmaceuticals of high specific activity, 16alpha-[77Br]bromoestradiol-17beta and 16alpha-[125I]iodoestradiol-17beta, has been carried out in immature female rats. The iodoestradiol has slightly higher uterine uptake at 1 hr after injection, whereas the brominated analog has significantly enhanced uptake at later times. The similar behavior of the two compounds in vivo suggests that estradiol labeled with I-123, Br-77, or Br-75 could be used interchangeably for the imaging of breast tumors containing estrogen receptors. In addition, coinjection 16alpha-[125I]iodoestradiol as an internal standard has been shown to be useful for comparison of different radiohalogenated estrogens. (Author abstract) (17 Refs)

24. 16ALPHA-[77BR]BROMOESTRADIOL: DOSIMETRY AND PRELIMINARY CLINICAL STUDIES.

McElvany KD, Katzenellenbogen JA, Shafer KE, Siegel BA, Senderoff SG, Welch MJ, Los Alamos Medical Radioisotope Group
Mallinckrodt Inst. Radiology, Washington Univ. Sch. Medicine, 510 South Kingshighway, St. Louis, MO, 63110
J Nucl Med; 23(5):425-430 1982

An estrogen-receptor-binding radiopharmaceutical, 16alpha-[77Br]bromoestradiol-17beta, has been used successfully at high specific activity to image carcinogen-induced mammary tumors in rats and in preliminary studies to image breast tumors in patients. The biodistribution of the labeled estrogen in rats and its clearance in a monkey were used to estimate the radiation absorbed doses to a human resulting from administration of the radiopharmaceutical. Preliminary imaging studies in patients with mammary carcinoma show promising results and warrant further development of radiolabeled estrogens, particularly those carrying positron emitters that could permit positron emission tomography - for example Br-75 or F-18. (Author abstract) (23 Refs)

25. E-17ALPHA-[125I]IODOVINYLESTRADIOL: AN ESTROGEN-RECEPTOR-SEEKING RADIOPHARMACEUTICAL.

Hanson RN, Seitz DE, Botarro JC
Dept. Medicinal Chemistry, Coll. Pharmacy and Allied Health Professions, Northeastern Univ., Boston, MA, 02115
J Nucl Med; 23(5):431-436 1982

Through the use of radioiododestannylation, the specifically labeled E-17alpha-[125I]iodovinylestradiol [(I-125)VE2] was synthesized rapidly and in high yield from the stable precursor E-17alpha-tributylstannylvinylestradiol (SnVE2), and its biodistribution was determined in immature female rats. The agent accumulated in the uterus, achieving a peak uptake of 0.465% ID-kg/g at 2 hr. Uterus-to-blood ratios of 19 and 16 occurred at 1 and 2 hr, respectively, declining to 7 by 4 hr after injection. The uptake of (I-125)VE2 by the uterus at 2 hr was reduced 58-65% by pretreatment of the immature rats with estradiol (5 ug) or tamoxifen (100 ug), and compared with 16alpha[125I]iodoestradiol, (I-125)VE2 showed greater uterine uptake and similar uterus-to-blood ratios. The ease of preparation of the radioligand represents an advantage over the synthetic procedures for other estrogen-receptor-seeking agents. (Author abstract) (26 Refs)

26. RADIOCHEMICAL PROBES FOR STEROID HORMONE RECEPTORS.

Toft DO, Wahner HW
Mayo Clinic, Rochester, MN
J Nucl Med; 23(5):451-453 1982

Measurement of steroid receptors in cancers, particularly breast cancer, is described and implications for cancer therapy discussed. Specific binding by radioactive hormone in tissue extracts is reliable but difficult to perform, especially in small tissue samples. Fluorescent estrogen analogs may be useful in the detection of receptors in breast cancer. Use of radiohalogenated steroids for receptor measurement appears promising. Safety and efficacy of the technic is considered. (11 Refs)

27. STEROID RECEPTORS IN HUMAN BREAST CANCER TISSUE.

Brentani MM, Pacheco MM, Oshima CT, Nagai MA, Goes JC
Laboratorio de Oncologia Experimental da Faculdade de Medicina da USP, Av. Dr. Arnaldo, 455-CEP 01246- S. Paulo, Brasil
Rev Latinoam Oncol Clin; 13(4):22-29 1981

Steroid receptors in a group of primary breast cancer patients were analyzed. Estrogen (ER), progesterone (PR), and glucocorticoid (GR) receptors were present in 60% of 350, 59% of 288, and 61% of 233, respectively, of the cancer patients. Frequency of ER, PR, and GR positivity was approx the same in pre- and postmenopausal women, but ER content was much higher in postmenopausal women. The likelihood of positive PR in a tumor increases with increasing ER content. The mean level of PR or GR decreases in tumors that lack ER. (20 Refs)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

28. BENZO(A)PYRENE-INDUCED EARLY CYTOPATHOLOGIC CHANGES AND PEROXIDASE ACTIVITY IN THE ENDOMETRIUM OF OVARIECTOMIZED RATS.

Kang YH, Bui-Tran MT, West WL
Dept. Pharmacology, Coll. Medicine, Howard Univ., Washington, DC, 20059
Toxicol Appl Pharmacol; 63(2):242-256 1982

The compound benzo(a)pyrene (BP) (50 mg/kg/day sc once a day for 3-6 days) induced mitosis, peroxidase activity, and focal squamous cell metaplasia in the endometrial epithelium of ovariectomized rats. Diethylstilbestrol (DES) (20 ug/kg/day sc for 3-6 days) administered alone did not produce significant ultrastructural changes in the endometrial cells of castrated rats but did induce peroxidase activity. Concomitant administration of DES and BP induced significant cytopathological changes. Thus, BP alone can induce metaplasia in rat endometrium without the involvement of ovarian hormones, and DES may enhance the cytotoxicity of BP, apparently by stimulating uterine peroxidase activity that may be involved in the metabolic activation of BP. (33 Refs)

29. DIFFERENTIAL EFFECT OF DEXAMETHASONE ON FRIEND LEUKEMIA CELLS INDUCED TO DIFFERENTIATE BY HEXAMETHYLENEBISACETAMIDE OR BUTYRIC ACID.

Gambari R
Inst. di Biologia Generale, Univ. di Roma, Rome, Italy
Cell Biol Int Rep; 6(4):341 1982

The effects of dexamethasone (DEX) on erythroid function in murine Friend leukemia (FL) cells, clone DS19-4, induced to differentiate by hexamethylenebisacetamide (HMBA) or butyric acid (BA) were investigated. Synthesis and translation of alpha- and beta-globin mRNA and Hb accumulation were greatly inhibited by DEX in the HMBA-induced cells. DEX had no effect on these functions in the BA-induced cells. The results suggest that HMBA and BA modulate gene expression in FL cells via a different mechanisms. The DS19-4 cells cultured with BA may share cellular properties in common with FL clones resistant to DEX inhibition of HMBA-induced erythroid differentiation. (5 Refs)

30. MECHANISMS OF INHIBITION OF MOUSE MYELOID LEUKEMIC CELL DIFFERENTIATION BY PROSTAGLANDIN F2ALPHA.

Takenaga K, Honma Y, Kado J, Hozumi M
(c/o Hozumi) Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Gan; 73(2):175-183 1982

Mouse myeloid leukemia M1 cells were induced to differentiate in vitro into macrophages and granulocytes by various inducers, including dexamethasone. Prostaglandin F2alpha inhibited the inductions by dexamethasone of phagocytic and lysozyme activities in M1 cells. Prostaglandin F2alpha stimulated the production of differentiation-inhibiting activity (I-activity) in M1 cells. I-activity production by prostaglandin F2alpha was decreased by simultaneous treatment with actinomycin D (5 ng/ml) but not with 5-fluoro-2'-deoxyuridine (10 ng/ml). The I-activity was inactivated by heating (70 C, 20 min) or by treatment with trypsin but not with mixed glycosidases or ribonuclease, suggesting that I-activity was due to a proteinous substance(s). B-Type prostaglandins also stimulated I-activity production, whereas A-, E- and D-type ones did not. Induction of I-activity by prostaglandin F2alpha was suppressed by simultaneous treatment with prostaglandin E2. Retinoic acid stimulated the synthesis and release of prostaglandin F2alpha and production of I-activity in M1 cells. Indomethacin completely inhibited induction of I-activity by retinoic acid. On the basis of these result, the relationship between I-activity production and prostaglandin F2alpha production is discussed. (Author abstract) (39 Refs)

31. THE DEXAMETHASONE-INDUCED INHIBITOR OF FIBRINOLYTIC ACTIVITY IN HEPATOMA CELLS. A CELLULAR PRODUCT WHICH SPECIFICALLY INHIBITS PLASMINOGEN ACTIVATION.

Coleman PL, Barouski PA, Gelehrter TD
Dept. Human Genetics, Univ. Michigan Medical Sch., Ann Arbor, MI, 48109
J Biol Chem; 257(8):4260-4264 1982

Dexamethasone induces an inhibitor of plasminogen-dependent fibrinolysis in rat hepatoma (HTC) cells. The specificity of the inhibitor for urokinase and plasmin was investigated using both fibrinolytic and esterolytic assays. Urokinase, but not plasmin, was inhibited by serum-free conditioned medium from cells incubated with 0.1 uM dexamethasone. The specificity of the inhibitor for plasminogen activator was demonstrated directly by the inhibition of the urokinase-catalyzed activation of 125I-plasminogen to 125I-plasmin. The inhibitory activity was stable to pH 3 for 2 hr at 37 C, a condition which inactivated fibrinolytic inhibitors in serum, suggesting a cellular origin for the inhibitor. Further evidence for the cellular origin was the constant daily production of inhibitor throughout a 4-day incubation with dexamethasone in serum-free medium. SF HTC-H1 cells, selected for their ability to grow in serum-free medium, were grown for 76 days (at least 30 generations) in the presence or absence of serum; dexamethasone induced equivalent amounts of inhibitory activity in cells which had been grown under both conditions. We conclude that the dexamethasone-induced inhibitor from HTC cells is a cellular product which is specific for the inhibition of plasminogen activation and which differs from other reported fibrinolytic inhibitors. (Author abstract) (36 Refs)

32. THE EFFECT OF DEXAMETHASONE ON THE INITIATION OF BETA-GLOBIN GENE TRANSCRIPTION IN DIFFERENTIATING FRIEND CELLS.

Mierendorf RC, Mueller GC
(c/o Mueller) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Biol Chem; 257(8):4496-4500 1982

Plasmid subclones of the 5' and 3' regions of the betamajor-globin gene have been used as probes to assay the level and character of the transcripts of this gene in differentiating Friend erythroleukemia cells treated with dexamethasone. Using an S1 nuclease protection protocol, it is shown that dexamethasone reduces the amount of precursor-specific sequences in differentiating Friend cells within 30 min without significantly affecting the nuclear turnover of these molecules. The sites of initiation and termination of transcription remained the same during the shutdown of transcription by the hormone. In contrast to the situation in Friend cells, dexamethasone failed to inhibit globin gene transcription in three normal erythroid tissues. The manner in which the Friend virus complex might render the globin genes sensitive to glucocorticoids is discussed. (Author abstract) (37 Refs)

33. EFFECT OF CHRONIC ADMINISTRATION OF A HIGHLY POTENT LHRH AGONIST ON PROSTATE SIZE AND SECRETORY FUNCTION IN GERIATRIC DOGS.

Vickery BH, McRae GI, Bonasch H
Dept. Physiology, Inst. Biological Sciences, Syntex Res. R2 - 101, 3401 Hillview Ave., Palo Alto, CA, 94304
Prostate; 3(2):123-130 1982

Following implantation of a pellet containing 125 or 170 ug/kg of D-Trp6 LHRH ethylamide into three geriatric dogs with palpable, subclinical, prostatic hyperplasia, the plasma levels of testosterone showed an initial rise for about a wk, followed by a rapid decrease. Plasma testosterone levels returned to pretreatment levels of 44 and 58 days after treatment in two dogs, but remained low through the 60-day study period in the third dog. Weekly pneumocystograms revealed a decrease in the prostate size after a lag period following the drop in testosterone levels. The change in prostate size was paralleled by a decline in ejaculate volume, a decrease in sperm motility, maturity and count. The effect on prostate size appeared to be reversible after discontinuation of treatment. Thus, LHRH agonists may have utility in the treatment of testosterone-dependent prostate pathology. (24 Refs)

34. INTERACTION OF CHALONES AND GLUCOCORTICOID HORMONES IN REGULATION OF CELL DIVISION.

Mamontov SG, Zakharov VB
N. I. Pirogov Second Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 93(2):51-52 1982

Interactions between the chalones and hydrocortisone (HC) were studied in C3HA mice with transplanted hepatoma 22a. Intact or adrenalectomized mice received a single or repeated injections of HC alone or in combination with chalone-containing liver extract. Analysis of cell proliferation in hepatoma 22a cells showed that chalone alone causes a 63.7% inhibition of mitotic activity, compared with 34.1% inhibition after single HC injection, 50.1% inhibition after repeated HC injection, and 61.0-72.4% inhibition after administration of chalone in combination with HC. Inhibitory effect of chalone was less pronounced in the adrenalectomized mice (45.2% inhibition of mitotic activity, compared with 63.7% inhibition in intact rats). These findings indicate that the expression of the inhibitory effect of chalone requires the presence of a certain level of adrenal cortex hormones in the blood. It was suggested that the type and the degree of interaction of chalones and glucocorticoid hormones depends upon the type of the target tissue. (12 Refs) (In RUS)

35. PROLACTIN STORAGE IN A CLONAL STRAIN OF RAT PITUITARY TUMOR CELLS IS CELL-CYCLE DEPENDENT.

Kiino DR, Burger DE, Dannies PS
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
J Cell Biol; 93(2):459-462 1982

GH4C1 cells (GH cells) are a clonal strain of rat pituitary tumor cells which secrete prolactin. We measured intracellular prolactin at different stages of the cell cycle using flow microfluorometry. Prolactin was stained by an indirect immunocytochemical technique using fluorescein isothiocyanate (FITC)-

conjugated antiserum, and DNA was stained simultaneously with propidium iodide. We found that prolactin storage in GH cells was cell-cycle dependent; prolactin storage increased as cells passed from G1 to S to G2 + M. We have shown previously that insulin and 17beta-estradiol act synergistically to increase intracellular prolactin three- to sevenfold and slow the rate of cell growth to approx 70% of control cells. In this study we observed that insulin and estradiol increased prolactin storage at each stage of the cell cycle but did not affect the cell-cycle distribution of the population even though cell growth was slowed. We conclude that insulin and estradiol did not increase prolactin storage by affecting the cell-cycle distribution of the population. (Author abstract) (13 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

36. ENHANCEMENT OF NITROSOUREA CYTOTOXICITY IN VITRO USING HYDROCORTISONE.

Tew KD, Wang AL, Lindner DJ, Schein PS
Div. Medical Oncology, Lombardi Cancer Center, Georgetown Univ., Washington, DC, 20007
Biochem Pharmacol; 31(6):1179-1180 1982

Colony forming potential (CFP) of HeLa cells following treatment with various concentrations of 2-[3-(2-chloroethyl)-3-nitrosoureido]-D-glucopyranose (CLZ) or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), with or without hydrocortisone-21-sodium succinate (HC) treatment is presented. CCNU was more toxic than CLZ, with all cells dead at 50 uM, irrespective of steroid pretreatment. The combination of HC pretreatment and CCNU decreased survival and CFP from 40% to 18% of control at 10 uM and 27% to 7% at 25 uM. The combination of CLZ and HC pretreatment produced enhanced cytotoxicity over CLZ alone at all concentrations of drug. Simultaneous administration of 10 uM HC with either nitrosourea resulted in an enhanced cell survival with CCNU and did not affect the cytotoxicity of CLZ. Thus, the scheduling was critical to cytotoxicity, with synergistic effects occurring only following HC priming. CLZ alkylation and carbamoylation into transcriptionally active chromatin could be linked to a disaggregation and overt relaxation of chromatin superstructure within the nucleus. This relaxation resulted in nuclear swelling, presumably mediated through nuclear matrix steroid receptors, which could function by altering the dynamic structural properties of the non-histone acidic protein scaffold of the nucleus. Presented data suggest that one or both of the nuclear targets (transcriptional chromatin and the nuclear matrix) may be important in determining the site-specific cytotoxic properties of nuclear reactant drugs such as nitrosoureas. (5 Refs)

37. CLONAL VARIANTS OF A MELANOMA CELL LINE SENSITIVE TO GROWTH INHIBITION BY DEXAMETHASONE.

Buzard RL, Hutchens TW, Hawkins EF, Markland FS, Horn D
Molecular Biology Div., Univ. Southern California, Los Angeles, CA, 90007
Exp Cell Res; 138(2):385-396 1982

We have isolated and characterized two clones of the RPMI 3460 Syrian hamster melanoma cell line which exhibit different responses to the synthetic glucocorticoid dexamethasone. In the presence of 10 nM dexamethasone, one clone (Clone 6) exhibits the growth inhibition, morphological alterations, and reduction in final cell density observed in the parental RPMI 3460 cell line. In contrast, the other clone (Clone 5), although exhibiting a reduction in final cell density, fails to exhibit the growth inhibition and morphological alterations. Thus, the effect of dexamethasone on growth and morphology can be expressed separately from the effect of dexamethasone on final cell density in these cells. This observation suggests that the two sets of responses can be controlled separately and that glucocorticoids may exert their influence through different or divergent biological pathways. In vitro receptor assays suggest that the different phenotypes of Clone 5 compared with Clone 6 cells cannot be explained by an absence of or reduction in cytosolic glucocorticoid receptor, in Clone 5 cells. Additional receptor characterization suggests that the different responses to dexamethasone of Clone 5 and Clone 6 cells do not reflect changes in the ability of receptor to exist in a stably activated form. Differences in the accumulation or depletion of extracellular components in the growth medium also do not seem to be responsible for the altered phenotype of Clone 5 vis-a-vis Clone 6 cells. (Author abstract) (42 Refs)

38. THERAPEUTIC AND PROGNOSTIC IMPLICATIONS OF GLUCOCORTICOID RECEPTORS AND TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE IN ACUTE LEUKEMIA.

Ho AD, Hunstein W, Ganeshaguru K, Hoffbrand AV, Brandeis WE, Denk B
Medizinische Universitats-Poliklinik, 6900 Heidelberg, W. Germany
Leuk Res; 6(1):1-8 1982

Glucocorticoid receptors (GR) were measured as binding of H3-dexamethasone in leukemic blasts from 23 patients with acute myeloid leukemia (AML) and 19 with acute lymphoblastic leukemia (ALL), and compared to response to chemotherapy. In addition, in vitro sensitivity of blasts to dexamethasone, and terminal deoxynucleotidyl transferase (TdT) activity were also measured in some cases. In AML patients median receptor level was 10,250 sites/cell, with a range of 0-17,649, and a dissociation constant ranging from 0.9-38.7 x 10-9M. In 11 AML patients tested there was no correlation between receptor level and in vitro sensitivity, and between response to chemotherapy and receptor level. TdT levels were within normal range for 12 patients investigated. In ALL patients receptor levels ranged from 1,433-26,858 sites/cell, with a dissociation constant ranging from 7.7-46.1 x 10-9M. There was significant in vitro sensitivity in 11/14 patients, but no correlation with in vivo sensitivity. TdT was high in 14 patients, and appeared to correlate with response. However, there was no linear correlation between GR levels and TdT activity. Usefulness of these measurements in identification and treatment of ALL is discussed. (32 Refs)

39. NON-GLUCOCORTICOID RECEPTOR-MEDIATED EFFECTS OF THE POTENT GLUCOCORTICOID DEACYLCORTIVAZOL.

Harmon JM, Schmidt TJ, Thompson EB
Lab. Biochemistry, Div. Cancer Biology and Diagnosis, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 42(6):2110-2114 1982

Deacylcortivazol (DAC), a potent glucocorticoid, contains a phenyl-pyrazole moiety fused to the 2-3 positions of the traditional steroid nucleus. When incubated with glucocorticoid-resistant mutants derived from the glucocorticoid-sensitive human leukemic cell line CEM-C7, DAC caused significant growth inhibition. However, this effect required 1 uM DAC, a concentration 50 times higher than that necessary for glucocorticoid receptor saturation. Cytotoxicity was observed in both mutants containing high-affinity glucocorticoid receptors defective in nuclear translocation and a mutant completely devoid of receptors. Further, in dexamethasone-resistant clones, DAC elicited only marginal increases in the activity of the glucocorticoid-inducible enzyme glutamine synthetase. Clones resistant to high concentrations of DAC could not be directly isolated from CEM-C7. However, stable DAC-resistant clones could be isolated from dexamethasone-resistant subclones of CEM-C7 with a frequency of 1 to 8 x 10(-4). These data are consistent with resistance to DAC being acquired in a two-step process. Our results suggest that the cytotoxicity of DAC at concentrations higher than necessary for glucocorticoid receptor saturation is not mediated by glucocorticoid receptors. Thus, DAC may be a bifunctional compound having both steroid receptor-mediated and receptor-independent cytotoxicity. (Author abstract) (28 Refs)

40. RESISTANCE TO L1210 MOUSE LEUKEMIA CELLS IN MODERATELY PROTEIN-MALNOURISHED BALB/C MICE TREATED IN VIVO WITH THYMOSIN FRACTION V.

Petro TM, Watson RR
Dept. Foods and Nutrition, Purdue Univ., West Lafayette, IN, 47907
Cancer Res; 42(6):2139-2145 1982

Moderate protein malnutrition retarded the ip proliferation of L1210 mouse leukemia cells in BALB/c mice. The increased resistance against leukemia cell growth in protein-malnourished mice was correlated with increased in vitro mitogenic responsiveness of spleen lymphocytes to phytohemagglutinin and increased levels of serum corticosterone but could not be correlated with altered development of splenic lymphocyte-mediated cytotoxicity. The increased resistance against leukemia cells in well-fed mice treated with thymosin alone could not be correlated with an increase in any of these parameters. Treatment with Thymosine Fraction V further increased the resistance of protein-malnourished mice to ip leukemia cell growth. The increased resistance of these mice to tumor cell growth was correlated with increased splenic lymphocyte mitogenic responsiveness to phytohemagglutinin, elevated serum corticosterone levels, and a slight increase in lymphocyte-mediated cytotoxicity 14 days after tumor challenge. For 7 days after the last treatment, protein-malnourished mice had reduced serum corticosterone levels. Nevertheless, the serum corticosterone levels were still higher than normal in these mice. (Author abstract) (34 Refs)

41. HORMONE SENSITIVITY OF THE R3327-G RAT PROSTATE ADENOCARCINOMA: GROWTH RATE, DNA CONTENT, AND HORMONE RECEPTORS.

Pollack A, Irvin GL, Block NL, Lipton RM, Stover BJ, Clafin AJ
Res. Service 151, Veterans Admin. Medical Center, 1201 N.W. 16th St., Miami, FL, 33125
Cancer Res; 42(6):2184-2190 1982

The growth of the R3327-G rat prostatic adenocarcinoma was significantly reduced when implanted in orchiectomized male rats (ORCH tumors). Tumors grown in intact animals (control tumors) had a doubling time of 7.4 days as compared to 9.2 days in ORCH tumors. A computer-based analysis of flow cytometric DNA histograms also detected significant differences between control and ORCH tumors. ORCH tumors were found to have 25% fewer cells with hyperdiploid DNA than control tumors (p less than 0.01). This androgen sensitivity in growth rate and the proportion of hyperdiploid cells were further reflected in the binding of [3H]methyltrienolone ([3H]R1881) to cytoplasmic (cytosol) and nuclear tumor extracts. ORCH tumor cytosols had a [3H]R1881 binding capacity which was 70% lower than controls (6071 fmol/g tumor tissue). Nuclear [3H]R1881 binding in ORCH tumors was undetectable in seven of eight samples while in control tumors, binding was detectable in five of six preparations. Sucrose density gradient analysis showed that cytosolic [3H]R1881 receptors sedimented at 8.1S in low salt and 4.6 to 3.3S in high salt. Nuclear [3H]R1881 receptors in high salt sedimented at 4.1 to 3.3S. Competition experiments using [3H]R1881 showed that [3H]R1881 receptors were primarily androgenic, although some displacement by estradiol did occur. In contrast, [3H]R1881 binding was found to be highly specific. The binding capacity of [3H]estradiol in ORCH tumor cytosols was 30% higher than controls (962 fmol/g tumor issue), while binding to ORCH and control nuclear extracts was similar. These data suggest that the inhibition of androgen-sensitive R3327-G tumor cells was related to the concentration of androgen receptors and that this in turn was expressed as a reduction in the proportion of hyperdiploid cells. (Author abstract) (33 Refs)

42. BIOLOGICAL BEHAVIOR OF MM1 HAMSTER MELANOMA.

Stanberry LR, Das Gupta TK, Beattie CW
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Cancer Res; 42(6):2238-2241 1982

We have reported evidence recently for a high-affinity receptor for glucocorticoid Malignant Melanoma Number 1 hamster melanoma and suggested that tumor growth was facilitated by adrenal steroids. This report characterizes the behavior of Malignant Melanoma Number 1 following manipulation of the pituitary-adrenal axis in vivo. Bilateral adrenalectomy significantly retarded tumor growth. Hypophysectomy also significantly reduced tumor growth. Silastic implants of hydrocortisone in intact hamsters produced a dose (7 to 28 ug/day)-related increase in tumor growth. Implants releasing a low dose (3 ug/day) of dexamethasone also increased tumor growth. Chronic exposure of adrenalectomized and intact hamsters to a high dose (125 ug/day) of desoxycorticosterone acetate also produced a significant increase over adrenalectomized and sham-adrenalectomized controls. In contrast, chronic administration of adrenocorticotrophic hormone and alpha-melanocyte-stimulating hormone to intact hamsters did not significantly alter melanoma growth. These observations support the suggestion that adrenocorticosteroids influence the growth of Malignant Melanoma Number 1 hamster melanoma and provide a model for studying the regulation of growth of a glucocorticoid-positive neoplasm originating outside the reticuloendothelial system. (Author abstract) (33 Refs)

43. PROMOTIVE EFFECTS OF STEROIDS AND BILE ACIDS ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE.

Cameron RG, Imaida K, Tsuda H, Ito N
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Cancer Res; 42(6):2426-2428 1982

The ability of four steroids and three bile acids to promote the appearance of hyperplastic foci and hyperplastic nodules initiated by diethylnitrosamine (DEN) in the liver of male Fischer rats was tested and compared with that of the known promoter phenobarbital (PB, 0.05%) as a standard value. Two weeks after a single dose of 200 mg of DEN per kg, the animals were exposed to test chemicals for 10 weeks. At 4 weeks following DEN, all treatment groups were subjected to partial hepatectomy. Of the steroids tested at the maximum tolerable doses, as determined in preliminary experiments, ethinyl estradiol was the most potent promoter, inducing more hyperplastic nodules than did PB and almost 50% less gamma-glutamyl transpeptidase-positive foci. However, gamma-glutamyl transpeptidase-positive foci induced by ethinyl estradiol were twice the average size as those induced by PB. The steroids testosterone, cortisone, and dexamethasone induced more foci than did DEN alone, but few if any hyperplastic nodules. Deoxycholic acid was the most potent promoter of the bile acids tested, inducing 3 to 4 times more hyperplastic nodules than did PB and more gamma-glutamyl transpeptidase-positive foci, which were 5 times larger on the average than those induced by PB. The other bile acids tested, lithocholic acid and taurine, induced slightly more foci than did DEN alone but no hyperplastic nodules. These findings suggest that ethinyl estradiol and deoxycholic acid are relatively strong promoters of the appearance of preneoplastic lesions in hepatocarcinogenesis. (Author abstract) (22 Refs)

44. GROWTH AND CELL SURVIVAL FOLLOWING TREATMENT WITH ESTRAMUSTINE, NOR-NITROGEN MUSTARD, ESTRADIOL AND TESTOSTERONE OF A HUMAN PROSTATIC CANCER CELL LINE.

Hartley-Asp B, Gunnarsson PO
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J Urol; 127(4):818-822 1982

Estramustine at concentrations ranging from 3-40 x 10(-6) M inhibited the cell growth and clonogenic survival of a human prostatic carcinoma cell line (DU 145). This cell line was found to be unresponsive to estradiol and testosterone at concentrations ranging from 10(-9) M to 5 x 10(-5) M. Metabolism studies with estramustine showed that only a few per cent of the ester linkage was cleaved during the exposure period. This small amount of metabolism could possibly lead to the release of nor-nitrogen mustard, which was however found not to be as inhibitory as estramustine in this cell line. The results indicate that estramustine per se causes the cell death of hormone unresponsive human prostatic carcinoma cells in cell culture. (Author abstract) (28 Refs)

45. ROLE OF NATURAL PROSTAGLANDINS IN THE CONTROL OF MURINE MAMMARY TUMOR VIRUS EXPRESSION.

Svec J, Svec P, Halcak L, Thurzo V
Cancer Res. Inst., Slovak Acad. Sciences, Csl. armady 21, CSSR-880 32 Bratislava, Czechoslovakia
J Cancer Res Clin Oncol; 103(1):55-67 1982

The regulation of murine mammary tumor virus (MuMTV) production by mammotropic hormones, hormonomimetic substances, and cyclic nucleotides was investigated. The virus produced in control and treated mammary tumor cell cultures was quantitated by measuring the supernatant reverse transcriptase activity in exogenous reaction using poly(rC).oligo(dG) as template-primer. Two days after exposure, the synthetic glucocorticoid, dexamethasone (DXMT), increased spontaneous MuMTV production at optimal concentration (0.1 umol) up to 10x. Dibutyryl derivative of cyclic AMP had no effect on spontaneous MuMTV production, whereas the drug potentiated suboptimal concentrations of the glucocorticoid. Natural prostaglandins, potent agonists of adenylate cyclase catalyzing intracellular synthesis of cyclic AMP, enhanced both basal (up to 5x) and DXMT-stimulated (up to 1.6 times) MuMTV replication. The MuMTV-stimulating activity of prostaglandins decreased in the order of PGA1 greater than PGE1 greater than PGB1 greater than PGF2 alpha. Prostaglandins can be replaced partially by norepinephrine and isoproterenol by enhancing the DXMT-mediated MuMTV stimulation, whereas these drugs remained without effect on spontaneous MuMTV production. Theophylline, an antagonist of cAMP-phosphodiesterase converting cAMP to AMP, enhanced the virus-stimulating activity of DXMT as well as of prostaglandins. The enhancement of MuMTV production by adenylate cyclase agonists do not correlate absolutely with the estimates of intracellular cAMP levels, since the highest amounts of cAMP have been repeatedly observed in cells treated with PGE1 and norepinephrine. The results indicate that besides hormones, other hormone-like substances and cyclic nucleotides may be involved in the complex mechanism of hormone-regulated MuMTV genome expression. (Author abstract) (55 Refs)

46. INTRALESIONAL CORTICOSTEROID INJECTION FOR INFANTILE ADNEXAL HEMANGIOMA.

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Am J Ophthalmol; 93(4):496-506 1982

I treated 10 patients who had adnexal hemangioma with intralesional injections of corticosteroid. A marked and lasting regression of the hemangioma occurred in eight of the patients and one had a moderate response. This treatment also proved effective in preventing amblyopia in infants who had large hemangiomas that occluded the visual axis, and often resulted in a reversal of the astigmatism induced by these tumors. There were no complications. The advantages of intralesional corticosteroid injection include ease of administration, speed of action, apparent freedom from adverse side effects, and repeatability. (Author abstract) (19 Refs)

47. MODULATION OF THE TOXICITY AND ANTITUMOUR ACTIVITY OF ALKYLATING DRUGS BY STEROIDS.

Shepherd R, Harrap KR

Dept. Biochemical Pharmacology, Inst. Cancer Res., Sutton, Surrey, Eng

Br J Cancer; 45(3):413-420 1982

The steroids prednisolone and progesterone significantly altered the therapeutic indices of the alkylating agents, nitrogen mustard, melphalan, cyclophosphamide, phenyl acetic mustard and chlorambucil. For nitrogen mustard, chlorambucil and phenyl acetic mustard, prednisolone reduced host toxicity in the rat and enhanced the antitumor effectiveness against alkylating-agent-resistant strains of the Yoshida sarcoma and Walker carcinosarcoma. Progesterone also increased the therapeutic index of chlorambucil in the rat by decreasing its systemic toxicity. Two other alkylating agents, melphalan and cyclophosphamide, exhibited lower therapeutic indices in combination with prednisolone against alkylating-agent-sensitive tumors. This was due to the greater host toxicity of the combination than of the alkylating agent alone. In alkylating-agent-resistant tumors, however, a significant increase in growth delay was achieved if prednisolone was combined with the alkylating agent. (Author abstract) (44 Refs)

48. EFFECT OF ESTRADIOL PROPIONATE AND PREGNANCY ON CARCINOGENESIS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN C3HA MICE.

Turusov VS, Murovannyi AN, Morozova OV
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):20-23 1982

The effects of pregnancy and estradiol propionate (EP) administration on 1,2-dimethyl hydrazine (DMH)-induced carcinogenesis were studied in female C3HA mice. Virgin or pregnant females were subjected to sc administrations of DMH (8 mg/kg/wk) alone or in combination with EP (10 ug/kg/wk). DMH and EP were given for 30 wk. Animals were followed up for 50 wk after the initiation of the experiment. DMH alone induced tumors in 75% of virgin mice and in 56.2% of pregnant mice. EP administration resulted in a marked increase of the incidence of colonic tumors (31.6%, compared with 8.3% after administration of DMH alone to virgin mice and 18.7% after administration of DMH alone to pregnant mice). Uterine sarcomas were observed in 28.9% of mice treated with DMH + EP, while all mice treated with DMH alone were free of uterine sarcomas. Hepatocellular tumors were observed only in mice treated with DMH + EP (23.7%). These findings indicate that EP can modify the DMH-induced carcinogenesis not only in the hormone dependent organs but also in the liver and in the colon. (14 Refs) (In RUS)

49. HUMAN PROSTATIC ADENOCARCINOMA: COMPARATIVE EXPERIMENTAL TREATMENT OF THE TUMOR LINE PC 82 IN NUDE MICE.

Hoehn W, Walther R, Hermanek P
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Prostate; 3(2):193-201 1982

The human prostatic adenocarcinoma PC 82, transplanted into male nude Balb/c mice, produced a newly developing tumor after 4-6 wk. These tumors had a doubling time of about 40 days, from which a volume doubling time of 12.5 days was calculated. Castration resulted in an immediate cessation of growth and a slight decrease in tumor size. Administration of 20 ug/day 17-beta-estradiol to intact males had a stronger effect on tumor progression, and a combination of estrogen + castration produced an even greater effect. Administration of 180 and 300 ug/day of estramustine phosphate (EP) resulted in a slight and variable decrease of the tumor growth rate; in some cases the tumor diameter increased after an initial growth regression. Combination of castration + EP produced a marked decrease in tumor size compared to the treatment with EP only. Administration of cyproterone acetate, in doses of 200 and 400 ug/day, and flutamide (SCH 13521) in a dose of 250 ug/day to intact mice resulted in a weak growth depression which was less than that caused by castration. The histological changes during tumor regression after treatment, eg widened acinar lumina, reduced epithelial height, and vacuolated cytoplasm, are comparable to features seen in treated human prostatic carcinoma. Thus, PC 82 may be a useful model system in comparative studies of new treatment modalities. (35 Refs)

50. EFFECT OF CORTICOSTEROIDS, VITAMINS, THIOPHOSPHAMIDE AND THEIR COMBINATIONS ON METABOLISM OF TUMOR-BEARING ANIMALS.

Dunaev VV
Dept. Pharmacology, Medical Inst., Zaporozhye, USSR
Farmakol Toksikol; 45(2):73-78 1982

The efficacy of hormone and vitamin therapy for the correction of metabolic disorders associated with the tumor growth was studied in random-bred male rats with transplanted carcinoma RC. Tumor-bearing rats received thiophosphamide (TP: 3 mg/kg) alone or in combination with nicotinic acid (NA: 10 mg/kg), folate (5 mg/kg), deoxycorticosterone (DOCA: 5 mg/kg), and hydrocortisone (HC: 10 mg/kg). The growth of carcinoma RC was associated with hyperfunction of the adrenal glands, hypertrophy and hyperplasia of the liver, and inhibition of the detoxicating function of the liver. On day 40-60 of tumor growth, the lactate/pyruvate coefficient for the liver tissue was 2x greater than that in the tumor-free controls. TP administration resulted in inhibition of the oxidative pathway of pyruvate transformation. HC, DOCA, NA, and folate reduced the inhibitory effect of TP on oxidative processes and thus decreased the lactate level in the liver tissue. (27 Refs) (In RUS)

51. INCREASED SURVIVAL DUE TO RADIOACTIVE ESTRADIOL IN MICE WITH C3HBA OR BW 10232 TUMORS.

Thysen B, Rettura G, Padawer J, Gatz M, Levenson SM, Seifter E
Dept. Lab. Medicine, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY, 10461
Cancer Chemother Pharmacol; 8(1):23-26 1982

The effect of graded doses of labeled and unlabeled estradiol (ED), when given in doses comparable to those used in physiologic and pharmacologic experiments, on C3HBA or BW 10232 tumor growth (TG) was studied in female C3H/HeJ and C57BL/6J mice. The effects of 1-5 uCi tritiated ED on TG and host survival in the C3HBA model are presented. Treatment for 4 days with tetralabeled tritiated ED resulted in approx 50% increase in mean survival time (ST). Host survival was not dose-dependent beyond 1 uCi, since ST achieved with 5 or 50 uCi was no better than that obtained with 1 uCi. The mean host survival of animals given 1,150 nanog unlabeled ED plus 50 uCi radioactive ED did not differ significantly from vehicle controls. No effect on host ST was found when comparable amounts of nonradioactive ED were administered for 4 days. Radioactive ED administration for 14 days at dosages of 0.2-2.0 uCi/day resulted not only in a significant increase in animal ST, but also in a significant inhibition of TG. When 0.2 uCi of radioactive progesterone (PG) or radioactive ED were injected per day to C57BL/6J female mice inoculated with BW 10232 tumor cells, TG rate was inhibited by 85% after only 2 days' treatment with [3H]ED. After 8 days' treatment, the inhibitory effect on TG rate declined to 36% and remained at this level until 12 days post hormone injection. As a result of radioactive ED administration for 14 days, ST in these tumor bearing mice was enhanced by 75%. Radioactive PG had no effect on these measurable parameters. Results indicated that further treatment with radioactive ED injections over a longer period of time may extend host survival as well as TG inhibition. (17 Refs)

52. TREATING METASTASIS WITH ESTRAMUSTINE PHOSPHATE.

Hoeft RT, Jones AG
Univ. Hosp. and Clinics, Madison, WI
Am J Nurs; 82(5):829-830 1982

After 3 mo therapy with estramustine phosphate (EP), 19/217 (9%) patients with estrogen-refractory, stage D prostate cancer showed partial response, 85/217 (39%) had stable disease, and 113/217 (52%) showed disease progression. EP is taken by mouth, has a low toxicity and, in some patients, rapidly relieves pain. The exact mechanism of action of EP is unknown. (3 Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

53. IMMUNOCHEMOTHERAPY FOR PROSTATIC CANCER.

Morishita N, Minami Y, Ihara K
Dept. Urology, Japan Red Cross Nagasaki Atomic Bomb Hosp., Nagasaki, Japan
Nippon Hinyokika Gakkai Zasshi; 72(8):973-978 1981

Four patients (61-82 yr old) with Stage D prostatic cancer (3 osteolytic bone metastasis, 1 osteoblastic bone metastasis and cranial nerve involvement) without prior hormone treatment and one patient (71 yr old) with Stage C prostatic cancer refractory to antiandrogen therapy were treated with combination immunotherapy. The immunotherapy, administered following castration, consisted of futraful (FT-207; 600 mg/day, ip), hexestrol (HX; 40 mg/day, ip), mitomycin C (MMC; 2 mg) combined with urokinase (6,000 units) 2x/wk (total 10 iv injections), and picibanil (OK-432; 1 IU, qod, im). Following induction of remission, HX (40 mg/day) was administered to one patient, and FT-207 (600 mg/day, ip) and polysaccharide-Kureha (PSK; 3g/day, ip) were administered to two patients. According to Ishida et al system of classification of results, marked effects of treatment were observed in 4/5 patients; calcification of osteolytic lesions was observed in three Stage D patients and disappearance of cranial nerve palsies in one Stage D patient. Complications included increased hepatic dysfunction (1 case) and anorexia (1). No changes in urocystograms were observed in 4/5 patients. (17 Refs) (In JPN)

54. IMMUNOMODULATORY EFFECTS OF OESTROGEN IN PROSTATIC CANCER: UPDATE AND FURTHER CONSIDERATION.

Ablin RJ
Div. Immunology, Cook County Hosp., Chicago, IL, 60612
Allergol Immunopathol (Madr); 9(1):63-70 1981

Recent experimental and clinical studies are reviewed which indicate that alterations of the endocrine environment may have profound effects on the immunogenicity of tumor and host responsiveness in patients with prostatic cancer (PC). A preliminary study in 123 PC patients subjected to cryosurgical prostatectomy suggested that there was a better clinical response and increased survival in those who did not receive hormonal therapy compared to those who did. Histological reactions were determined in pre- and post-surgical prostate tissue biopsies of 37 of these patients for whom there had been clinical indications for biopsy. The inflammatory reactions observed, characterized by granuloma, eosinophils (ES) and lymphocytes (LM), or plasma cells (PLC) correlated with three favorable findings: (1) superior survival, 73% (11/13) with LM or PLC and 86% (6/7) of patients with ES vs 50% survival in patients without these infiltrates; (2) infiltrates were observed only in patients with well differentiated, moderately well differentiated or cribriform patterns; and (3) the absence of cancer in 57% (4/7) of patients with ES, 47% (7/15) of patients with LM or PLC, and 1 patient with granuloma vs presence of cancer in 88% (7/8) of patients in which tissue was unchanged from pre-cryosurgical biopsies. Histological changes were also correlated with hormonal therapy (estrogens and/or orchiectomy). It is suggested that the inflammatory infiltrates might represent a local antitumor immune reaction following cryosurgery. (34 Refs)

55. ADJUVANT THERAPY IN TREATING INFECTIONS.

Hara K
Second Dept. Internal Medicine, Nagasaki Univ. Sch. Medicine, Nagasaki, Japan
Nippon Kagaku Ryoho Gakkai Zasshi; 30(1):108-111 1982

The immunological removal of pathogens from the host organism and its significance for adjuvant therapy were discussed with respect to patients cancer. Study of humoral immunity in patients with lung cancer who were treated with steroids, anticancer agents, radiotherapy, etc, showed high levels of IgG in Stage 3 and 4 patients, and the pretreatment levels did not change after treatment. This indicated that, barring hereditary or secondary hypoglobulinemia, humoral immunity was no problem in the advanced stage cancer patients. Comparison of 57 lung cancer patients with 36 healthy controls indicated that chemotaxis of neutrophils in the patients was significantly decreased and the decrease was related to the stage of the disease. Macrophage chemotaxis was erratic in the cancer patients prior to treatment, but the administration of picibanil tended to improve chemotaxis of monocytes in the patients. Depressed monocyte chemotaxis was associated with poor prognosis of the patients. Cellular immunity was also decreased in the lung cancer patients compared to that in the healthy controls. Use of picibanil to stimulate cellular immunity and muramyl-dipeptide to stimulate phagocytosis in two patients with cancer (maxillary gingival carcinoma and small cell anaplastic carcinoma, respectively) was reported. (no Refs) (In JPN)

GENERAL REVIEWS ON STEROID HORMONES

56. THE ROLE OF IMMUNOSUPPRESSANTS IN LYMPHOCYTE FUNCTION.

Winkelstein A
Dept. Medicine, Montefiore Hosp., Pittsburgh, PA, 15213
The Handbook of Cancer Immunology Volume 6: Lymphoid Cell Subpopulations-Structure, Function, and Interactions. Waters H, ed. New York, Garland STPM Press, 314 pp., 1981.

Effects of cytotoxic drugs on lymphocyte numbers, functional activities, and immunosuppressive properties are discussed. Such effects are closely correlated with the drugs' cell cycle specificities. Specific agents discussed include azathioprine, cyclophosphamide, methotrexate, and chlorambucil. Humoral and cell-mediated responses, toxicities, and use of corticosteroids are considered. (128 Refs)

57. GYNECOLOGIC TUMORS.

Perez CA, Knapp RC, Young RC
Div. Radiation Oncology, Washington Univ. Sch Medicine, Mallinckrodt Inst. Radiology, St. Louis, MO
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

The relative roles of surgery, radiotherapy (RT), and combinations of surgery and RT in the treatment of cervical carcinomas, endometrial adenocarcinomas, uterine mixed mesodermal tumors and sarcomas, Fallopian tube carcinomas, and clear cell carcinomas of the vagina or cervix are discussed. Surgery (with or without adjuvant RT) is the major treatment for the early stages of these diseases and RT for Stages III-IV. In patients with endometrial cancer, responses to progestational hormones are related to age, disease-free interval, and tumor histology. Responses to single-agent chemotherapy (doxorubicin is the most effective agent thus far identified) are unrelated to age, disease-free interval, tumor histology, sites of metastases, or previous treatment. Surgery is the major treatment for carcinomas, premalignant diseases, or melanomas of the vulva and RT for carcinomas of the vagina. RT for nonmalignant gynecologic diseases increases the risk of leukemia and ovarian or uterine malignancies. In patients with Stage I-II gestational trophoblastic tumors, the initial treatment is hysterectomy or methotrexate (MTX), regardless of risk factors (human chorionic gonadotropin titers, ovarian size, type of pregnancy, age, coagulopathy, trophoblastic embolization, and hyperthyroidism), depending on the patient's desire for further pregnancy. Actinomycin D, cyclophosphamide or chlorambucil, and perhaps other agents may be added if gonadotropin titers remain high despite MTX therapy. Hydroxyurea, vincristine, and doxorubicin are used in one of the combination protocols (CHAMOCA) given to Stage IV patients. (446 Refs)

58. CANCER OF THE BREAST.

Hellman S, Harris JR, Canellos GP, Fisher B
Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Epidemiology, pathology, classification of tumor types, tumor characteristics, local and regional spread, staging, theories on the spread, pretreatment evaluation, screening, and treatment of breast cancer are reviewed. Conservative surgery and/or radiotherapy (RT) and radical mastectomy (with or without RT) are about equally effective local treatments. Treatment of Stage III disease requires a combination of effective local treatment (usually RT) and systemic therapy. Menstrual status, extent of disease, and the tumor's estrogen receptor (ER) content should be used to select candidates for endocrine therapy (additive or ablative), antiestrogen, and chemotherapy. Combinations of cyclophosphamide with 5-fluorouracil and methotrexate or adriamycin are the most effective cytotoxic regimens. Patients with extensive, rapidly progressive metastases seldom respond to endocrine therapy and should be given chemotherapy. In other cases, the sequence of administration of endocrine therapy and chemotherapy is unrelated to survival. Endocrine therapy may be effective in patients with ER-positive tumors who relapse after chemotherapy, but second-line chemotherapy tends to be ineffective. Sequential administration of alternating non-cross-resistant cytotoxic regimens does not improve the occurrence or duration of remissions. Recurrences may consist of cross-resistant cell lines. A combination of vinblastine and mitomycin C may be useful against these refractory relapses. Further progress in therapeutic research will require continuing admission of patients to clinical trials. Since systemic therapy is palliative in most patients with advanced disease, potentially effective new treatments may be given to patients in symptomatic early relapse from the best first-line chemotherapy. Diagnosis and treatment of lobular breast cancer in situ and of breast cancer in males are discussed. (396 Refs)

59. RESEARCH ON THE MENOPAUSE.

WHO Scientific Group on Research on the Menopause, Bancroft J, Burger HG, Devi PK, Mack TM, Nordin BE, Nylander P, Ryan KJ, Sas M, Sinnathuray TA
World Health Organization, Geneva, Switzerland
WHO Tech Rep Ser (670): 120 pp., 1981.

The controversy over the existence of a menopausal syndrome of somatic and psychological symptoms and illness and the lack of data on the age distribution of menopause (MP) and on menopausal sociocultural significance in developing countries are discussed. The endocrinology of MP, age distribution, sociocultural significance of MP in different settings, symptoms associated with MP, disorders resulting from or possibly accelerated by MP, risks of therapeutic estrogens and progestins to peri- and postmenopausal women with particular reference to neoplasia, fertility-regulating methods for women approaching MP, and estrogens and the health care management of peri- and postmenopausal women are reported. Summaries of three studies of endometrial carcinoma conducted before 1975 and of case-control studies of endometrial cancer (EC) with epidemiological details are presented. Two major areas of ignorance in regard to risks of EC associated with estrogen therapy are the persistence of the oncogenic effect, and the nature of the dose-response curve at low doses and duration of use. Epidemiology of breast cancer (BC) is even more suggestive of endocrine origins than that of EC. Risk is related to a variety of endocrine phenomena, including ages at menarche, MP, and first pregnancy. Early oophorectomy has long been recognized to be strongly protective. Cohort studies and case-control studies of estrogen therapy and BC are presented. Several mechanisms for the relationship between endogenous hormones and BC have been proposed. Both naturally occurring and synthetic estrogens and progestins appear under some circumstances to be carcinogenic for BC in animal species. (383 Refs)

60. HYPERTENSION CAUSED BY ADRENAL LESIONS: THE ROLE OF THE ADRENAL GLAND IN HYPERTENSION.

Gross MD
Nuclear Medicine Service, Veterans Admin. Medical Center, 2215 Fuller Road, Ann Arbor, MI, 48105
Urol Radiol; 3(4):233-235 1982

Adrenal hypertension syndromes are reviewed, including Cushing's syndrome, primary aldosteronism, adrenal enzyme defects, and pheochromocytoma. The disorders are classified as originating either in the cortex or medulla. Detection of the cancerous growth underlying these conditions begins with observation of adrenal hormone excesses they induce. Therapies are evaluated for each of the syndromes. (9 Refs)

61. METHOTREXATE GUIDELINES--REVISED.

Roenigk HH, Auerbach R, Maibach HI, Weinstein GD
Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL, 60611
J Am Acad Dermatol; 6(2):145-155 1982

Revised guidelines for the use of methotrexate (MTX) in psoriasis are presented, including some new and/or controversial information. Criteria for patient selection, recommended

MTX dosage schedules, drug interactions influencing therapy (including systemic corticosteroids, which should be avoided if possible), the commonly observed side effects,toxicity to the liver, kidneys, and lungs, MTX absorption patterns (which may fluctuate from wk to wk), the risks of subsequent malignancy and genetic damage (which appear to be low after MTX treatment is stopped), and the use of MTX in pustular psoriasis are discussed. (51 Refs)

62. GLUCOCORTICOID RECEPTORS AND THEIR ROLE IN ONCOLOGY.

Smirnova KD, Gershtein ES, Bassalyk LS
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (3):61-68 1982

Distribution of glucocorticoid receptors (GCR) in normal tissues and various tumors is discussed, with special emphasis on the prognostic role of GCR assay in cancer hormone therapy. GCR were detected in breast neoplasms, soft tissue sarcomas, kidney tumors, melanomas, thymomas, and leukemic cells. Sensitivity of breast cancer to glucocorticoids was shown to be associated with the presence of GCR. GCR determination increases the prognostic efficacy of estrogen receptors (ER) assay. Of 23 patients with GCR- and ER-positive breast neoplasms, 19 responded to the hormone therapy. Analysis of GCR levels in children with acute lymphoblastic leukemia showed that the patients with greater than 6,000 GCR sites/cell had longer remissions than the patients with less than 2,500 GCR sites/cell. In contrast, the increased level of GCR in the adult patients with chronic lymphocytic leukemia was associated with more rapid disease progression. (59 Refs) (In RUS)

OTHER RELATED STUDIES

63. CONCOMITANT SECRETION OF CALCITONIN, BETA-ENDORPHIN AND ACTH FROM MEDULLARY THYROID CARCINOMA IN VIVO AND IN VITRO.

Lamberts SW, Hackeng WH, Visser TJ
Dept. Internal Medicine III, Erasmus Univ., Rotterdam, The Netherlands
Eur J Cancer Clin Oncol; 18(3):253-260 1982

The present study was performed to investigate the possible synthesis of a common precursor molecule for calcitonin (CT), adrenocorticotropin (ACTH) and beta-lipotropin (beta-LPH)/beta-endorphin (beta-EP) by the human medullary thyroid carcinoma (MTC). In a patient with MTC but without Cushing's syndrome, the response of plasma CT, ACTH and cortisol levels to a calcium infusion, lysine vasopressin (LVP) and dexamethasone were measured. A parallel increase of these hormones in response to calcium and LVP was seen, while there was a paradoxical increase of CT during dexamethasone infusion. Incubation of MTC fragments obtained at surgery showed a significant correlation of the secretion of CT, ACTH and beta-LPH/beta-EP in response to calcium, LVP and dexamethasone. The concomitant release of these hormones in vivo and in vitro could be compatible with the synthesis of a common precursor molecule for CT, ACTH and beta-LPH/beta-EP in MTC, although this was not substantiated by gel-chromatography of the tumor extract. Corticotropin releasing factor, a regulator of the normal processing of pro-opiococorticoid precursor molecule in the anterior pituitary gland, is also able to activate ACTH, beta-LPH/beta-EP and calcitonin secretion from the malignant C-cell of the thyroid. (Author abstract) (42 Refs)

64. GONADOTROPIN-RELEASING HORMONE ANALOGUES FOR PROSTATE CANCER: UNTOWARD SIDE EFFECTS OF HIGH-DOSE REGIMENS ACQUIRE A THERAPEUTICAL DIMENSION.

Jacobi GH, Wenderoth UK
Urologische Klinik und Poliklinik im Klinikum, Johannes-Gutenberg-Universitat, Langenbeckstrasse 1, D-6500 Mainz, W. Germany
Eur Urol; 8(3):129-134 1982

Gonadotropin-releasing hormone (Gn-RH), a hypothalamic decapeptide, mediates the synthesis and release of pituitary luteinizing hormone (LH). Synthetic Gn-RH analogues with prolonged duration of action are therapeutically administered with 'pro-fertility' intention to overcome endogenous Gn-RH deficiency, ie hypogonadotropic hypogonadism and related disorders. When Gn-RH analogues are chronically administered in high supraphysiological dosages, however, a paradoxical effect of pituitary overstimulation becomes evident: gonadotropin release is reduced, Leydig cell responsiveness is impaired, and testosterone secretion is blocked to castrate levels. Metabolic mechanisms involved include desensitization of the pituitary to Gn-RH, down-regulation of Gn-RH receptors, the depletion of the releasable LH pool, the breakdown of physiological feedback mechanisms, as well as direct interactions of the Gn-RH analogue with the Leydig cell. It is tempting to assume that, on the basis of this untoward side effect, high dose Gn-RH analogues will acquire a therapeutical dimension in the palliative treatment of prostate cancer. The therapeutical effect of castrate levels of testosterone is achieved without orchiectomy, cardiovascular side effects of estrogens are avoided, and the drug is conveniently applicable via the pernasal route. From the data available today Gn-RH analogues in overstimulatory dosage can be expected to be safe and effective in the palliative treatment of prostate cancer and would thus prove a true alternative to conventional contrasexual measures. (Author abstract) (35 Refs)

65. PULMONARY TOXICITIES OF DRUGS.

Yin B
Dept. Internal Medicine, First Affilitated Hosp., Human Medical Coll., Changsha, People's Republic of China
Zhonghua Jiehe He Huxixi Jibing Zazhi; 4(3):183-186 1981

Although less frequently seen than gastrointestinal and skin reactions, pulmonary toxicities are sometimes quite serious and may be fatal. Pulmonary toxicities due to various types of drugs and their associated signs, symptoms and clinical findings are reviewed. Drugs covered include antibiotics, corticoids, oral contraceptives and anticancer agents such as busulfan, bleomycin, methotrexate and cyclophosphamide. (18 Refs) (In CHI)

66. TISSUE DAMAGE DUE TO EXTRAVASATED DEPOSITION OF DOXORUBICIN.

Trope C, Thiseus S, Jacobsson S, Palmer B, Johnsson JE
Onkologiska kliniken, Lasarettet, S-221 85 Lund, Sweden
Lakartidningen; 79(17):1686-1688 1982

The observation of tissue damage due to deposition of extravasated doxorubicin in 14 patients (1 man, 2 boys and 11 women, 5-80 yr old) with carcinoma of the urinary bladder, breast, ovaries, uterus, liver, and with osteosarcoma and acute lymphocytic leukemia is reported. Doxorubicin was always administered together with other cytostatics. The injection sites were in the back of the hand, forearm, and elbow. Seven of the patients required no surgical treatment for the tissue damage (local inflammation at the injection site or necrosis).

The quantity of extravasated doxorubicin was calculated to be 4-10 mg in 5/7 patients, and was unknown in 2/7. Two patients were not treated at all, four were treated with hydrocortisone injections, one with physiological saline solution. Surgical treatment for the tissue damage was necessary in the other seven patients along with hydrocortisone treatment in 3/7 and with injections of physiological saline solution in one. The quantity of extravasated doxorubicin was calculated to be 15-60 ml in 6/7 patients and was unknown in 1/7. To avoid tissue damage due to deposition of doxorubicin, the drug should never be injected in previously irradiated or lymphedematous regions, and the backs of the hands and feet and the elbow should not be selected as injection sites. The injections should be given first in distant sites. The cytostatics should be administered intermittently in the infusion. (11 Refs) (In SWE)

67. SEPTIC ARTHRITIS DUE TO CANDIDA SPECIES IN PATIENTS WITH CANCER: REPORT OF FIVE CASES AND REVIEW OF THE LITERATURE.

Fainstein V, Gilmore C, Hopfer RL, Maksymiuk A, Bodey GP
M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Rev Infect Dis; 4(1):78-85 1982

Five patients (4 men, 1 woman; 18-68 yr) who developed septic arthritis due to Candida species while receiving chemotherapy for various malignancies are reported. The affected joint was the knee in all patients, and all developed synovial effusions. Three patients were receiving antibiotics and corticosteroids in addition to antineoplastic therapy. All patients had iv catheters, and three also had indwelling urinary catheters. Three patients were severely neutropenic (WBC less than 1,000/mm(3)). C albicans and C tropicalis were responsible for three and two infections, respectively. C tropicalis infection was cured in one patient by a course of po ketoconazole and in the other by treatment with amphotericin B and miconazole. C albicans arthritis was cured in one of two patients treated with amphotericin B; prior treatment with both ketoconazole and miconazole failed. The third patient with C albicans arthritis died of disseminated disease despite amphotericin B therapy. Candida arthritis in cancer patients is usually an indication of disseminated disease and should be treated with aggressive systemic antifungal agents. (30 Refs)

68. GYNECOMASTIA AFTER CYTOTOXIC THERAPY FOR METASTATIC TESTICULAR CANCER.

Turner AR, Morrish DW, Berry J, MacDonald RN
Cross Cancer Inst., 11560 University Ave., Edmonton, Alberta T6G 1Z2, Canada
Arch Intern Med; 142(5):896-897 1982

Four men with metastatic nonseminomatous testicular cancer, who had received combination chemotherapy, experienced transient gynecomastia. Serum hormone levels were measured during and after the resolution of the gynecomastia. These levels indicated toxic effects on Leydig's cells and germinal epithelium concurrent with raised serum estradiol levels in the absence of tumor. The gynecomastia may have been caused by Leydig's cell dysfunction or refeeding after substantial wt loss. This benign form of gynecomastia must be recognized to avoid unnecessary investigation and treatment. (Author abstract) (28 Refs)

69. THE PHARMACOKINETICS OF HIGH-DOSE MEDROXYPROGESTERONE ACETATE (MPA) IN THE THERAPY OF ADVANCED BREAST CANCER.

Blossey HC, Bartsch HH, Kanne D, Koebberling J, Nagel GA
Dept. Medicine, Univ. Goettingen, Robert-Koch-Strasse 40, Goettingen D-3400, W. Germany
Cancer Chemother Pharmacol; 8(1):77-81 1982

The pharmacokinetics of medroxyprogesterone acetate (MPA: 1.5 mg/day, po) was investigated in 16 patients with advanced breast cancer. Initial phase kinetics revealed two groups of patients differing in the time needed to reach the plateau state: a first group exhibiting steady plasma levels of MPA within 5 days and a second group whose plateau was reached after 2 wk of treatment. There was a broad intra- and interindividual variation of MPA plasma levels in the plateau state which were dependent neither on the frequency of MPA determination nor on the duration of observation. These variations are probably a result of individual differences in drug absorption, distribution, and metabolism. Mitomycin C, which was part of the therapy schedule, had no effect on the actual plasma concentrations or on the plateau state. The plateau concentrations were very sensitive to dose modifications; there was a rapid decrease in MPA plasma levels following dose reduction or cessation of therapy. The elimination kinetics showed two phases, with half-times of about 20 hr and 3-4 days. Of three different solvents (diethyl ether, petroleum ether, and benzene:isooctane) used for extraction of MPA in the absence of MPA metabolites, diethyl ether was the most efficient. There was an excellent linear correlation between determination in plasma and ether extracts over a wide range of concentrations, suggesting that direct plasma RIA without extraction may be valid for assaying MPA in pharmacokinetic studies. (35 Refs)

70. ENDOCRINE THERAPY OF BREAST CANCER.

Powles TJ
St. George's Hosp., Tooting, London SW17, England
Breast Cancer Management: The Experience of the Combined Breast Clinic, St. George's Hospital/The Royal Marsden Hospital. Coombes RC, Powles TJ, Ford HT, and Gazet JC, ed. London, Academic Press, 317 pp., 1981.

Hormone receptors and types of endocrine treatment for breast cancer are discussed. Endocrine treatment of breast cancer includes treatment with estrogens, oophorectomy, androgen therapy, anti-estrogen therapy, adrenalectomy, hypophysectomy, aminoglutethimide, progestins, and danazol. Although the response of metastatic breast cancer to endocrine therapy occurs in only approx 30% of patients, the quality and duration of response is better than for chemotherapy. With new agents, the toxicity is less than in chemotherapy and such agents are usually administered more easily. Patients with bone and soft tissue metastases should always be considered for endocrine therapy. (21 Refs)

71. INHIBITION OF SYNTHESIS OF ALPHA-FETOPROTEIN BY GLUCOCORTICOIDS IN CULTURED HEPATOMA CELLS.

Chou JY, Mano T, Feldman M
Pregnancy Res. Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD, 20205
J Cell Biol; 93(2):314-317 1982

Alpha-fetoprotein (AFP) synthesis was studied in the presence and absence of glucocorticoids in rat hepatoma Mc-A-RH-7777 cells. Radioimmunoassay of media from cell cultures grown in the presence of glucocorticoid (dexamethasone or cortisol) showed a reduction in AFP, an increase in albumin, and no significant change in transferrin accumulation, as compared to controls. Labeling experiments with L-[35S]methionine indicated that in both cells and media of dexamethasone-treated cultures there was a 50-80% reduction in polypeptide precipitated by anti-AFP serum, as compared with controls; no change was seen in polypeptide precipitated by anti-transferrin serum. Pulse and pulse-chase experiments demonstrated that dexamethasone inhibited the synthesis of AFP but not its secretion. The half-time for secretion of AFP in the presence and absence of dexamethasone was 43 min. (Author abstract) (21 Refs)

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HORMONES IN CANCER-RELATED BIOLOGY

Steroid Hormones

SERIES CB07 No. 82/10 OCTOBER, 1982

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. DEFECTIVE 11 BETA HYDROXYLATION IN PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA DUE TO 21 HYDROXYLASE DEFICIENCY.

Kolanowski J, Crabbe J
Endocrine Unit, Univ. Louvain (UCL 5530), B-1200 Brussels, Belgium
Ann Endocrinol (Paris); 42(6):537-538 1981

The 11-beta-hydroxylation step was assessed in seven patients with congenital adrenal hyperplasia (CAH) due to partial block of 21-hydroxylation, by means of simultaneous measurements of plasma 11-deoxycortisol (S) levels, 17-hydroxyprogesterone (17-OH-P), cortisol (F), and corticosterone (B) in baseline conditions as well as during corticotropin (ACTH) or metyraprone (MP) administration. Baseline plasma steroid levels (nanomole/liter) were 221 +-43 for F, 43.6 +-9.1 for S, 410 +-85 for 17-OH-P, and 22.7 +-7.3 for B. With reference to normal values, a 50 to 100-fold increase in plasma 17-OH-P existed with plasma F reduced to half of normal values, confirming the partial block of 21-hydroxylation. Plasma S was

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more than one order of magnitude higher than in normal subjects, indicating the existence of a defect in 11-beta-hydroxylase. Upon infusion of ACTH (250 ug tetracosapeptide iv over 8 hr), plasma F increased to 468 +-58 nanoM (nM), while plasma S increased to 102 +-39 nM. Following MP administration to three patients, plasma S did not exceed 221 +-30 nM, thus confirming that the activity of 21-hydrolase was reduced. Additional evidence for partial insufficiency of 21-hydroxylation was provided by the fact that plasma B reached only 46 +-13 nM upon ACTH infusion vs 170 +-17 nM in normal subjects. The rise in plasma 17-OH-P was considerably more marked in patients with CAH. (4 Refs)

2. FREQUENCY OF ABNORMALITIES OF CORTISOL SECRETION AND WATER METABOLISM IN PATIENTS WITH SMALL CELL CARCINOMA OF THE LUNG AND OTHER MALIGNANCIES.

Trump DL, Abeloff MD, Hsu TH
Wisconsin Clinical Cancer Center, Madison, WI, 53792
Chest; 81(5):576-580 1982

Twenty-eight patients with small cell carcinoma of the lung (SCCL) before therapy were compared with 28 patients with other malignancies (13 breast carcinoma, 5 gastrointestinal cancer, 7 lymphoma, 4 other lung cancers) for adrenal function by measuring 8 AM plasma cortisol, 8 AM to 4 PM diurnal plasma cortisol variation, and dexamethasone (1 mg) suppression of 8 AM plasma cortisol, and for water metabolism by a standard water loading test. These tests were abnormal in 8/28 (28.5%), 20/28 (71%), 5/20 (25%), and 12/20 (60%) of SCCL patients, respectively, as compared to 4/20 (18%), 13/20 (70.5%), 6/18 (29.5%), and 15/22 (68%) of patients with other malignancies, respectively. There were no statistical differences between the groups for any of the tests. When survival was evaluated SCCL patients with abnormal dexamethasone suppression had statistically significant (P less than 0.05) shorter survival than the same patients with a normal test. In the patients with other cancers abnormal results in all three tests correlated with shorter survival: 8 AM plasma cortisol (0.05 less than p less than 0.075); diurnal variation (p less than 0.001); and dexamethasone suppression (p less than 0.025). SCCL patients do no appear to have increased disturbances in water and cortisol metabolism as compared to patients with other types of cancers. (20 Refs)

3. OXIDATIVE METABOLISM OF THE SYNTHETIC ESTROGENS HEXESTROL AND DIENESTROL INDICATES REACTIVE INTERMEDIATES.

Metzler M, McLachlan JA
Inst. Pharmacology and Toxicology, Univ. Wurzburg, Versbacher Strasse 9, D-8700 Wurzburg, W. Germany
Adv Exp Med Biol; 136(partA):829-837 1982

Oxidative metabolism of meso-hexestrol (HES) and alpha-dienestrol (E,E-DIES) was studied in rats to determine whether electrophilic intermediates are formed from these estrogens. Chemical structures of HES metabolites in the glucuronide fraction in HES-treated rats are presented. For two of the metabolites, 1-hydroxy-HES and 3'-hydroxy-HES, authentic reference compounds were available to confirm their structure. Metabolic fate of HES comprises hydroxylation at the aromatic rings followed by methylation, hydroxylation at the terminal methyl group of the hexane chain, and combinations of these metabolic steps. No indication for the conversion of HES into diethylstilbestrol was found. When the biliary glucuronides of E,E-DIES-treated rats were analyzed, the predominant compound was unchanged E,E-DIES. Three major metabolite peaks in the gas chromatogram had mass spectra indicative for the formation of an olefinic epoxide; one peak could represent the epoxide itself, while the other two peaks might denote rearrangement products. The oxidative biotransformation of E,E-DIES appears to involve olefinic epoxidation in addition to catechol formation, although the extent of metabolic oxidation of E,E-DIES is rather low as compared to HES. (11 Refs)

4. UNSPECIFIC CHANGES IN TUMORMAKERS UNDER HIGH-DOSE PROGESTERON-THERAPY IN PATIENTS WITH DISSEMINATED BREAST CANCER (MEETING ABSTRACT)

Kleeberg UR, Purfurst CH, Peters A, Treidler J
Hamatologischonkologische Praxis Altona, Max-Brauer-Allee 52, D 2000 Hamburg 50, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A19 1982

In a prospective, randomized study of the AIO (Association of Internal Oncology) (GOMC II) we treated 50 women with terminal disseminated breast cancer, following prior endocrine and cytostatic chemotherapy with high dose Progesterone (1500 mg MAP po daily) and Aminoglutethemid (100 mg AG po daily). Weekly progress controls of tumormarkers and hepatic enzymes showed a significant increase in patients with objective tumor remission, no matter whether they had or had not liver metastases. These unspecific antigen- and enzymefluctuations under HD- MAP/AG-therapy therefore cannot be taken as an indication for further tumor progress. It has been shown by additional studies that these marker-fluctuations are due to Progesterone-induced changing of liver function and lipid-metabolism. (no Refs)

5. TAMOXIFEN INHIBITS LEYDIG CELL STEROIDOGENESIS: IN VIVO AND IN VITRO STUDIES.

Lin T, Murono EP
Medical Service, William Jennings Bryan Dorn Veterans Hosp., Columbia, SC, 29201
Metabolism; 31(6):543-547 1982

The effects and mechanism of action of tamoxifen (TAM) on steroidogenesis in Leydig cells of mature Sprague-Dawley rats were investigated. Hypophysectomized rats were treated with 0, 10, or 100 ug TAM suspended on 0.1 ml corn oil. Twenty-four hr later, tail blood samples were obtained, followed by administration of 5 units/100 g body wt human chorionic gonadotropin (HCG) sc. Two hr later, rats were sacrificed, trunk blood collected, and sera separated and stored. TAM in a dose of 10 ug had no effect on HCG-stimulated testosterone in 21 day old hypophysectomized rats formation, while 100 ug TAM did reduce HCG-stimulated testosterone synthesis significantly. TAM had no effect upon basal testosterone levels in 60 day old hypophysectomized rats. After HCG stimulation, there was a 46% reduction in mean plasma testosterone levels in rats treated with 10 ug TAM and 69% reduction in rats treated with 100 ug TAM. When decapsulated testes from these rats were incubated for 3 hr, rats treated with 100 ug TAM produced significantly less testosterone when compared to rats treated with either 10 ug TAM or controls. TAM thus directly inhibits testosterone response to gonadotropin stimulation both in immature and mature hypophysectomized rats. Conversion of pregnenolone to testosterone was blocked by TAM. Both estrogen and TAM inhibited leuteinizing hormone-stimulated testosterone formation, but with different patterns of inhibition. TAM had no effect upon HCG binding to gonadotropin receptors, or upon adenylate cyclase activity. These results indicate that TAM blocks multiple steps in steroidogenesis. (29 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

6. EFFECTS OF ESTROGEN ADMINISTRATION ON SERUM TESTOSTERONE IN COPENHAGEN RATS.

Grossman HB, Kleinert EL, Herr HW, Whitmore WF
Section Urology, Univ. Michigan Medical Center, 1405 East Ann St., Box 03, Ann Arbor, MI, 48109
Prostate; 3(3):225-229 1982

Diethylstilbestrol phosphate (DES-P) was given ip or po to mature male Copenhangen rats, and its effect on serum testosterone determined by radioimmunoassay. In untreated rats, testosterone levels were 252 +-128 nanog/ml (mean plus standard deviation), while in castrated animals the levels were consistently below 10 nanog/ml. Oral DES-P at levels of 0.8 and 1.6 ug/ml of drinking water consistently depressed serum testosterone from days 8-66. Suppression was variable during the first wk. Initial suppression was lower with treatment at 0.4 ug/ml, but castrate levels of serum testosterone were reached by day 12 and maintained for more than 30 days. Av fluid intake was 38 ml/day by animals on po DES-P. With a single ip dose of 0.50 mg DES-P, rats developed prompt suppression of serum testosterone, with return to control values in 2 wk. The rate of return was variable. Similar results were seen with 0.25 mg, with a greater variability of suppression. Limited data with multiple 1.0 or 0.5 mg doses indicate that suppression was more complete and prolonged than at the lower doses. Testosterone suppression may be useful clinically in following response to estrogen therapy. (4 Refs)

7. ABSENCE OF INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN MICE AFTER TOPICAL APPLICATION OF BECLOMETHASONE DIPROPIONATE.

Goos CM, Houben JJ, Hukkelhoven MW, Van Ginneken CA, Vermorken AJ
Res. Unit Cellular Differentiation and Transformation, Univ. Nijmegen, Geert Grooteplein Noord 21, 6525 EZ Nijmegen, The Netherlands
Res Commun Chem Pathol Pharmacol; 36(2):319-327 1982

The effects of topical application of beclomethasone dipropionate (a corticosteroid) on the aryl hydrocarbon hydroxylase (AHH) activity in epithelial tissue (lung and skin) were studied. To evaluate the results of the pre-treatment with beclomethasone dipropionate a comparison was made with the effects of the topical application of benzanthracene (a polycyclic aromatic hydrocarbon and a known inducer of AHH activity). AHH activities were increased 2.5 to 5-fold in lung and about 20-fold in skin of mice after topical application of benzanthracene. However, after pre-treatment with beclomethasone dipropionate no induction of AHH activity could be observed, either in lung or in skin. The implications of these findings are discussed. (Author abstract) (8 Refs)

8. UNCONJUGATED STEROIDS IN LEIOMYOMAS AND TUMOR-BEARING MYOMETRIUM.

Otubu JA, Buttram VC, Besch NF, Besch PK
(c/o P. K. Besch) Reproductive Res. Lab., St. Luke's Episcopal Hosp., Houston, TX, 77030
Am J Obstet Gynecol; 143(2):130-133 1982

The concentrations of 17beta-estradiol, progesterone, and estrone in leiomyomas and tumor-bearing myometrium were determined by specific radioimmunoassays in hysterectomy specimens from 12 women aged between 30 and 47 yr. The concentration of 17beta-estradiol was significantly higher in leiomyomas than in myometrium. There was no difference in the concentration of progesterone in leiomyomas and myometrium. There was no difference in the concentration of progesterone in leiomyomas and myometrium. The concentration of estrone was higher in the myometrium than in the leiomyomas, although the difference was not statistically significant. The concentrations of progesterone, 17beta-estradiol, and to some extent estrone show variation with the phase of the menstrual cycle. The significance of the difference in concentration of 17beta-estradiol in leiomyomas and myometrium, the relationship of this difference to the concentrations of estrogen and progesterone receptors, and factors possibly related to the growth of leiomyomas are discussed. (Author abstract) (16 Refs)

9. FAMILIAL PROSTATIC CANCER RISK AND LOW TESTOSTERONE.

Meikle AW, Stanish WM
Div. Endocrinology and Metabolism, 50 North Medical Drive, Salt Lake City, UT, 84132
J Clin Endocrinol Metab; 54(6):1104-1108 1982

We investigated whether familial factors influence (1) the incidence of prostatic cancer and (2) the plasma content of sex steroids. A 4-fold higher relative risk for the development of prostatic cancer was observed for brothers (n = 257) of prostatic cancer cases (n = 150) compared to their brothers-in-law (n = 202) and males in the general population of the state of Utah. The intraclass correlation for plasma testosterone content [intraclass correlation coefficient (r1) = 0.51; P less than 0.01] and the apparent free testosterone concentration (r1 = 0.54, P less than 0.01) were highly significant in nonendocrinologically treated cases and their brothers. Further, sons and their fathers had significant intraclass correlations for both plasma dihydrotestosterone (r1 = 0.83; P less than 0.01) and the ratio of testosterone to dihydrotestosterone (r1 = 0.46; P less than 0.05). Probands and their brothers, and sons of the patients with the disease had significantly lower plasma testosterone levels than controls of comparable age. This is the first documentation indicating that familial (possibly genetic) factors are potent risk factors for predisposing men to the development of prostatic cancer and in regulating the plasma content of androgens. Our results indicate that plasma androgen levels in families with prostatic cancer are clustered in the lower range of the normal population. They also suggest that plasma androgen content is more similar within each family with the cancer than among the families without cancer. (Author abstract) (17 Refs)

10. THE EFFECTS OF ORCHIDECTOMY, ESTROGENS, AND CYPROTERONE ACETATE ON PLASMA TESTOSTERONE, LH, AND FSH CONCENTRATIONS IN PATIENTS WITH CARCINOMA OF THE PROSTATE.

Varenhorst E, Wallentin L, Carlstrom K
Dept. Urology, Univ. Hosp., Linkoping, Sweden
Scand J Urol Nephrol; 16(1):31-36 1982

The peripheral plasma concentrations of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were determined in 46 patients (age 51-86 yr) with cytologically confirmed prostatic carcinoma. Treatment consisted of subcapsular orchidectomy (15 cases) or estrogen medication (16 cases) or cyproterone acetate (15 cases). The determinations were made before and 2 wk and 2 mo after treatment was initiated. No correlation was found between the pretreatment levels of testosterone and gonadotrophins and the local extent of the primary tumor or the degree of malignancy. Nor was there any correlation between hormonal level, presence of metastases or patient age. Orchidectomy and estrogen medication both resulted in very low plasma testosterone levels, corresponding to 15% of the pretreatment values. This proportion was 28% in the group treated with cyproterone acetate. Orchidectomy was followed by significant increase in the levels of LH and FSH. Estrogen treatment resulted in suppression of the LH levels to 40% and of FSH to 14% of the pretreatment values. The corresponding decreases in response to cyproterone acetate were 65 and 35%. The results indicate that reduction in gonadotrophin secretion is the primary mechanism in the lowering of testosterone levels produced by treatment with estrogens or cyproterone acetate. (Author abstract) (45 Refs)

11. PERIPHERAL VENOUS CONCENTRATIONS OF OESTROGENS IN POSTMENOPAUSAL WOMEN WITH OVARIAN CANCER.

Heinonen PK, Tuimala R, Pyykko K, Pystynen P

Dept. Obstetrics and Gynecology, Univ. Central Hosp., Tampere, Finland

Br J Obstet Gynaecol; 89(1):84-86 1982

Serum concentrations of estrone, estradiol and estriol were measured in 23 postmenopausal women, 12 with ovarian cancer and 11 with genital prolapse. Estrone (387.6 pmol/l) and estradiol (72.7 pmol/l) levels were higher in the cancer group than those in the control group (159.8 and 27.5 pmol/l respectively), while estriol levels did not differ (434.5-270.8 pmol/l). The results indicate abnormal ovarian function in postmenopausal patients with ovarian cancer. (Author abstract) (11 Refs)

12. EFFECTS OF TOTAL AND SUBCAPSULAR ORCHIDECTOMY ON SERUM CONCENTRATIONS OF TESTOSTERONE AND PITUITARY HORMONES IN PATIENTS WITH CARCINOMA OF THE PROSTATE.

Bergman B, Damber JE, Tomic R

Dept. Urology, Univ. Umea, S-901 85 Umea, Sweden

Urol Int; 37(2):139-144 1982

Twenty-two men with carcinoma of the prostate were consecutively subjected to either total or subcapsular orchidectomy at random. Serum concentrations of testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone and testosterone-estrogen-binding globulin were followed. No differences were found between the two groups during the 6-mo follow up period. Orchidectomy reduced testosterone concentration in all cases and none responded to human chorionic gonadotrophin stimulation 6 mo postoperatively. The concentrations of free and bound testosterone were calculated but did not vary between the two types of operation, which were considered equally efficient in reducing testosterone concentration. However, doubts about the completeness of the operation might possibly arise in cases with cancer progress and therefore we prefer total orchidectomy as the first choice, but perform subtotal orchidectomy on those men preferring this type of operation psychologically. (Author abstract) (20 Refs)

13. THE SITE OF ACTION OF AMINOGLUTETHIMIDE (AG) IN ADVANCED BREAST CANCER (MEETING ABSTRACT)

Harris AL, Dowsett M, Jeffcoate S, Smith IE

Royal Marsden Hospital, Fulham Road, London, England

Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Short Synacthen tests (250 ug Synacthen IM) were performed on 10 post-menopausal women with advanced breast cancer who had received AG 250mg 4 x day plus hydrocortisone 20mg 2 x day for at least 3 months. There was no significant rise in cortisol, estrone or dehydroepiandrosterone sulphate. However, 17OH progesterone (17OHP), delta 4 androstenedione (delta 4A) and dehydroepiandrosterone rose markedly. 17OPH rose by up to 53 fold, and delta 4A up to 10.8 fold. This pattern of response to ACTH suggests that there is little inhibition of desmolase by AG, but that inhibition of aromatase is more important and even a marked rise in precursors does not overide aromatase inhibition. Since conventional dose AG is given to inhibit desmolase we used low dose AG without hydrocortisone to inhibit aromatase, which in vitro is more sensitive than desmolase. Twelve postmenopausal patients were given AG 125mg 2 x day for 1 week and in all patients estrone fell (50% of baseline). AG was then doubled each week until 500 mg 2 x day. Estrone at the highest dose of AG was 54 of baseline. The addition of 20mg hydrocortisone 2 x day did not further suppress estrone (55% of baseline). This suggests that adrenal suppression by hydrocortisone does not contribute to the effect of AG and that low dose AG alone should be assessed for therapeutic effect. (no Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

14. LEIOMYOMAS: STEROID RECEPTOR CONTENT. VARIATION WITHIN NORMAL MENSTRUAL CYCLES.

Soules MR, McCarty KS

Duke Univ. Medical Center, Box 3711, Durham, NC, 27710

Am J Obstet Gynecol; 143(1):6-11 1982

In an attempt to clarify further the relationship between ovarian function and uterine leiomyomas, we investigated the cytoplasmic estrogen and progesterone receptor content in these uterine tumors. The study population consisted of 17 women of reproductive age at various stages of ovulatory menstrual cycles. Serum samples were analyzed for estrogen and progesterone content; tissue samples from endometrium, myometrium, and leiomyomas were analyzed for cytoplasmic estrogen and progesterone receptor content. The levels of cytoplasmic estrogen and progesterone receptor in leiomyomas demonstrated the same quantitative and qualitative cyclic changes throughout the menstrual cycle apparently in response to variations in circulating estrogen and progesterone as found in endometrium and myometrium. (Author abstract) (16 Refs)

15. MULTIPLE SIMULTANEOUS AND SEQUENTIAL ESTROGEN RECEPTOR VALUES IN PATIENTS WITH BREAST CANCER.

Peetz ME, Nunley DL, Moseley HS, Keenan EJ, Daveport CE, Fletcher WS
(c/o Fletcher) Dept. Surgery, Div. Surgical Oncology, Oregon Health Sciences Univ., 3181 S.W. Sam Jackson Park Road, Portland, OR, 97201
Am J Surg; 143(5):591-594 1982

Fifty-nine women had multiple estrogen receptor assays done, either simultaneously or sequentially. Eight-six percent of the patients who had multiple synchronous estrogen receptor assays from various metastatic sites showed no significant discrepancy in estrogen receptor values. When estrogen receptor assays were done sequentially without intervening therapy, 83.5% of the patients maintained their initial positivity or negativity. However, when the second estrogen receptor determination was preceded by either chemotherapy or hormonal therapy, 33% of the patients had a significant discrepancy in estrogen receptor values. The most common discrepancy was estrogen receptor-positive tumors becoming estrogen receptor-negative, although a small number of patients were found whose receptor values became more positive after hormonal ablation. (Author abstract) (18 Refs)

16. DECREASED NOCTURNAL PLASMA MELATONIN PEAK IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER.

Tamarkin L, Danforth D, Lichter A, DeMoss E, Cohen M, Chabner B, Lippman M
NIH, Building 6, Room 136, Bethesda, MD, 20205
Science; 216(4549):1003-1005 1982

Plasma melatonin concentrations were determined over a period of 24 hr in 20 women with clinical Stage I or II breast cancer. In 10 of the patients, whose tumors were estrogen receptor positive, the nocturnal increase in plasma melatonin was much lower than that observed in 8 control subjects. Women with the lowest peak concentration of melatonin had tumors with the highest concentrations of estrogen receptors. A significant correlation was found between the peak plasma melatonin concentration and the tumor estrogen receptor concentration in 19 of the patients. These data suggest that low nocturnal melatonin concentrations may indicate the presence of estrogen receptor positive breast cancer and could conceivably have etiologic significance. (Author abstract) (18 Refs)

17. DOPAMINE RECEPTORS IN THE RAT PITUITARY AND THE TRANSPLANTABLE PITUITARY TUMOR MTTF4: EFFECT OF CHRONIC TREATMENT WITH OESTRADIOL.

Andre J, Marchisio AM, Morel Y, Collu R
U. E. R. Lyon-Nord INSERM U 34, Hopital Debrousse, 29 Rue Soeur Bouvier, 69322 Lyon Cedex 1, France
Biochem Biophys Res Commun; 106(1):229-235 1982

The compound 3H-spiroperidol was shown to bind to crude membrane preparations from rat pituitary tumor MtTF4. The binding kinetics were similar to those with normal pituitary membranes. Competition experiments using d- and l-butaclamol, bromocriptine, and dopamine indicated the dopaminergic nature of the binding sites of MtTF4 membranes. A 15-day estradiol treatment caused a marked decrease of the concentration of these receptors in the tumor but only a slight decrease in the pituitary. These results suggest that estradiol might selectively modulate the action of dopamine in various tissues. (14 Refs)

18. CORRELATION BETWEEN TYROSINE HYDROXYLASE ACTIVITY, MELANOGENESIS, AND ESTRADIOL BINDING IN HUMAN MELANOMA CELLS.

Hakim AA
180 Longwood Drive, Kankakee, IL, 60901
Res Exp Med (Berl); 180(2):99-115 1982

The relationship between estradiol-binding proteins in cytosol fractions of in vitro cultured human malignant melanoma cells to the estradiol receptor in human mammary carcinoma cells was explored. Three cell lines derived from patients with malignant melanoma were used: HMMC-ShA, HMMC-WJP and HMMC-ZBJ. The human mammary carcinoma lines employed were HMCC-SE, HMCC-BS, HMCC-GM, and HMCC-KM. Cytosol fractions from mammary carcinoma cells, or malignant melanoma cells, and tyrosine hydroxylase (TH) bind 3H-estradiol (3HE) with strong affinity. To differentiate the binding between the various neoplastic cells, use was made of monoclonal antibodies secreted by cloned cell hybrids which were formed by the fusion of murine myeloma cells with spleen cells from BALB/c mice pre-immunized with purified TH. The monoclonal TH-antibodies inhibited the enzymic activity and binding of 3HE to TH or to the cytosol fraction of melanotic melanoma cells but had no effect on such binding to cytosol fractions from various mammary epithelial or mammary carcinoma cell lines. Cultivation of estradiol-responsive melanotic melanoma cells in media supplemented with TH-antibodies caused loss of pigmentation, the cells became amelanotic and non-responsive to 17beta-estradiol. The study thus indicates that estrogen does not bind to melanoma cells via a receptor as for mammary carcinoma cells, but to tyrosine hydroxylase. (66 Refs)

19. ESTROGEN RECEPTOR ASSAY ON BREAST CANCER MICROSAMPLES. IMPLICATIONS OF PERCENT CARCINOMA ESTIMATION.

van Netten JP, Algard FT, Coy P, Carlyle SJ, Brigden ML, Thornton KR, To MP
(c/o Algard) Dept. Biological Sciences, Univ. Victoria, Victoria, B.C., V8W 2Y2, Canada
Cancer; 49(11):2383-2388 1982

Forty-milligram strips of malignant breast tissue were divided longitudinally into 20-mg microsamples. Soluble protein concentration was determined for one-half, and histologic evaluation for viable carcinoma content was made on its sister half. The correlation coefficient for 88 such comparisons was 0.330. This suggests that estrogen receptor (ER) assays that do not take into account the actual amount of carcinoma present in the sample may not permit reliable stratification of ER data. Using this technique, ER values obtained for 129 breast tumor microsamples were adjusted to reflect carcinoma content. A comparison of ER values before and after such adjustment revealed that the relative status of 73% was not significantly changed. The ER status of 27%, however, was changed sufficiently to be of potential clinical significance. (Author abstract) (19 Refs)

20. ESTROGEN RECEPTOR HETEROGENEITY AND THE RELATIONSHIP BETWEEN ESTROGEN RECEPTOR AND THE TRITIATED THYMIDINE LABELING INDEX IN HUMAN BREAST CANCER.

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Oncology; 39(4):197-200 1982

Tissue from 54 patients with breast cancer was analyzed for estrogen receptor (ER). From 38 patients, tissue from multiple tumor sites was analyzed to determine ER heterogeneity. In 13 patients (34%) both positive and negative ER values were obtained. ER negative (ER-) results were observed more frequently in metastatic lesions. In 28 patients both the ER and [3H]-thymidine labeling index (LI) were measured in the same lesion. [3H]-Thymidine was administered in vivo. There was a positive correlation between ER positivity and low LI. The mean LI of 8 ER positive (ER+) tumors was 3.4 in contrast to a mean LI of 10.0 for 14 ER-tumors (p less than 0.01). LI of 6 mixed ER tumors (E+/-) was intermediate (mean 5.7). High LI (greater than or equal to 8) was associated with decreased survival regardless of the stage of disease at the time of study. ER with LI may provide an improved basis for treatment selection. (Author abstract) (17 Refs)

21. A STUDY OF ANDROGEN RECEPTOR-DNA INTERACTION BY DNA CELLULOSE DISSOCIATION KINETICS (MEETING ABSTRACT)

Buttyan R, Bland L, Schaffer R, Olsson CA, Kallos J
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Although endocrine treatment is a dominant form of therapy for patients with prostatic carcinoma, steroid receptor content measurements have not been predictive of which patients will benefit from such treatment. To better understand the mechanism of hormonal responsiveness and to analyze the nature of interaction between androgen receptor complex (AR) and the genome, we have developed an in vitro approach to study AR-DNA interactions by measuring the dissociation rate of 3H-AR from DNA-cellulose. Cytoplasmic AR (labelled by incubating a 100,000 x g supernatant of rabbit prostate cytosol with 10-8M 3H R1881 followed by ammonium sulfate precipitation) was allowed to bind to DNA cellulose for 45 minutes at 4 C. Subsequently the dissociation rate of AR from DNA-cellulose was measured by the loss of radioactive AR from DNA-cellulose pellets. At 0 time, soluble DNA was added to start the reaction and aliquots were taken at different time intervals (from 0 to 30 min) to determine the radioactivity remaining in the DNA-cellulose pellet. The dissociation rate of AR in the absence of soluble DNA was extremely slow. In the presence of soluble DNA, however, the half-life of the AR-DNA complex was approximately 20 min. The rate of dissociation was shown to be a sensitive measure of the stability of the initial AR-DNA complex; more stable complexes dissociate more slowly. (no Refs)

22. NUCLEAR ESTROGEN BINDING IN HORMONALLY AND NON-HORMONALLY INDUCED RENAL CARCINOMA (MEETING ABSTRACT)

Sufrin G, Alvarez J, Swaneck G
No affiliation given
77th Annual Meeting of the American Urological Association, Inc; May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Animal models of Renal Carcinoma (RC) have been described and the estrogen induced RC of the hamster is a unique example of a hormonally induced and hormonally dependent neoplasm. Since a critical requirement of estrogen responsive tissue is estrogen binding to their nuclei, we studied nuclear estrogen binding in this tumor and in RC induced in rats by the non-hormonal drug streptozotocin. RC was obtained from male hamsters after continuous (8-10 months) treatment with diethylstilbestrol (DES) (total dose, 300mg) and from male Wistar Furth rats 9-11 months following a single injection of streptozotocin (65 mg/kg). Purified renal nuclei were isolated and nuclear estrogen binding measured using a tritiated estradiol (3HE2, 98Ci/mmol) exchange assay. Specific binding was determined by subtracting total from non-specific binding. Saturation analysis of hamsters RC nulcei showed a 6-10 fold increase in the amount of 3HE2 specifically bound as compared to nuclei from untreated animals. In contrast, no increase 3HE2 binding was observed when abdominal muscle nuclei or liver nuclei from DES treated animals were compared to muscle or liver nuclei from untreated controls. The amount of 3HE2 bound by nuclei from streptozotocin induced RC showed no change as compared to untreated controls. Moreover when renal nuclei from Wistar Furth rats who were treated with DES for 8 months and who do not develop RC in response to chronic DES were compared to untreated controls, no change in 3HE2 binding was noted. The estrogen induced and estrogen dependent hamster RC exhibits binding characteristics associated with estrogen target tissue and with other estrogen dependent tumors. (no Refs)

23. CLINICAL USEFULNESS OF HISTOCHEMICAL ANDROGEN BINDING SITE DETERMINATION IN PROSTATIC ADENOCARCINOMA (MEETING ABSTRACT)

Macchia RJ, Pertschuk LP
New York Prostatic Binding Site Group, Brooklyn, NY
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

A test has been devised by Pertschuk which semi-quantitatively measures androgen binding sites in prostatic tissue. This paper is a report on the results of a clinical trial conducted to determine the usefulness of this test in predicting which patients with prostatic adenocarcinoma will respond to hormonal manipulation. The test itself is a histochemical one in which frozen sections (4 microns thick) of prostatic tissue are incubated with a solution of fluorescein tagged androgen for 2 hours. A semi-quantitative estimate of binding site density is then made using an ultraviolet microscope. When sufficient tissue was available quantitative biochemical determination of androgen receptors was also undertaken. The clinical trial was designed as follows. All patients with prostatic adenocarcinoma from whom tissue was removed were enrolled in the study. All pertinent clinical data was entered into a computerized data retrieval system. No clinician was aware of the results of the androgen binding site assay. The assayist was not aware of any clinical data. Determination of objective response to therapy was made by application of the published criteria of the National Prostate Cancer Project. To date, 270 patients have been entered into the study. Of these, 40 with previously untreated stage C or D disease have been followed for 2 or more years. A statistically significant correlation was demonstrated between the histochemical test and response to therapy which exceeded that of the biochemical test. (no Refs)

24. MENSTRUAL CYCLE DEPENDENT VARIATIONS OF BREAST CYST FLUID PROTEINS AND SEX STEROID RECEPTORS IN THE NORMAL HUMAN BREAST (MEETING ABSTRACT)

Silva JS, Wells SA, Georgiade NG, Dilley WG, McCarty KS, McCarty KS
Duke University Medical Center, Durham, NC
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Normal breast and endometrium have distinct menstrual cycle dependent variations in morphology. While menstrual cycle variations of estrogen receptor (ER) and progesterone receptor (PR) have been reported for human endometrium, studies of the breast have been hampered by a lack of samples from a 'normal', non-diseased population. Two glycoproteins, gross cystic disease fluid protein (CDP) and non-receptor progesterone binding protein (PBP) were shown to correlate with ER, PR and degree of breast carcinoma differentiation. We analyzed extracts for ER, PR, PBP and CDP in 56 strictly-defined normal breast tissues. Receptors were quantitated by SDGA for ER or DCCA for PR. Radioimmunoassay was used to quantitate, levels of CDP and PBP. Menstrual cycle dependence was observed for ER, PR, CDP and PBP. Mean ER levels were significantly higher during days 3-7 than at other times in the cycle, as was the number of specimens with ER greater than 3 fmole/mg protein. Higher PR levels and PR values greater than 10 were noted more frequently during day 8-14 than other periods. Both CDP and PBP had significantly increased mean values during day 8-14, low levels days 15-20 and intermediate levels for the other intervals. The cyclic variations in CDP and PBP suggest that these proteins may be useful as indicators of intact ER control. These data also indicate that until sex steroid receptor variations during the menstrual cycle are more fully characterized, it would seem prudent to evaluate the ER status of premenopausal patients by sampling their tumors during the proliferative phase of the menstrual cycle. (no Refs)

25. CLINICAL SIGNIFICANCE OF NUCLEAR ANDROGEN RECEPTORS (ARN) IN PROSTATE CANCER (MEETING ABSTRACT)

Mohla S, Davis JL, Jackson AG, Kovi J, Hunter JB, Ahmad J, Jones G
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Med Pediatr Oncol; 10(1):98 1982

The objectives of this study were to evaluate retrospectively (a) the importance of nuclear androgen receptors in patients with prostatic carcinoma in determining the clinical response of these patients to endocrine therapy; (b) the possible correlation of nuclear androgen receptors with tumor differentiation and (c) the comparison of ARn in patients with benign and malignant prostatic disease. Nuclear androgen receptors were quantitated in 40 malignant and 35 benign specimens using protamine sulfate. Sixty-three percent (26/41) of carcinomas were well differentiated (WD) while 24% and 12% were moderately well differentiated (MWD) and poorly differentiated (PD), respectively. ARn (greater than 50 fmoles/g tissue) were detected in 75% of malignant and 77% of benign neoplasms, respectively; there was no correlation between tumor grade and ARn. The mean ARn levels were higher in benign than in malignant neoplasms. ARn presence was independent of ARc (cytosolic androgen receptors); 75% (14/19) of ARc positive (greater than 3 fmoles/mg protein) and 76% (16/21) of ARc negative patients, respectively, had greater than 50 fmoles/g tissue of ARn. Twenty-nine patients have been evaluated for the relationship between ARn and the clinical response to endocrine therapy. Eighteen of 21 patients (86%) with ARn greater than 50 fmoles/g tissue responded favorably to endocrine therapy. In those patients with ARn less than 50 fmoles/g tissue the response was only 25% (2/8). These preliminary results indicate that nuclear androgen receptors may be clinically useful in selecting patients for endocrine therapy. (1 Ref)

26. COMPARISON OF CLINICAL RESPONSE TO HORMONE THERAPY USING ESTROGEN RECEPTOR ANALYSES BY BIOCHEMICAL VERSUS HISTOCHEMICAL METHODS (MEETING ABSTRACT)

McCarty KS, Nichols DE, Leight G, Cox LE, Georgiade G, Ferguson BJ, Reintgen D, Hiatt K, McCarty KS, Seigler HF
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Lab Invest; 46(1):53A 1982

Techniques for sex steroid receptor analysis by histologic means must be validated relative to standard techniques and clinical response. Estrogen receptor analyses by the standard sucrose density gradient technique (SDGA) and DCCA were compared with estradiol-17-HEM-BSA-FITC(17E), E2-6-CMO-BSA-FITC (6E), and poly E2-anti-E2-FITC (PEP) localization on serial sections of 70 metastatic breast cancers from patients who were treated by hormone therapy. Clinical evaluation was double blind relative to fluorescent E2-binding studies (mean follow-up, 2 years). SDGA (8S) gave the best predictive value of a positive of clinical response. Three histochemical methods relative to standard techniques gave sensitivities of PEP, 53 per cent; 6E, 48 per cent; 17E, 86 per cent with specificities of PEP, 45 per cent; 6E, 57 per cent; and 17E, 48 per cent. Comparing histochemical techniques to clinical response revealed a predictive value of a positive below that predicted by chance alone, despite impressive cytoplasmic/nuclear localization on sections with apparently appropriate displacement qualities. (no Refs)

27. IMMUNOHISTOLOGIC DEMONSTRATION OF ESTROGEN RECEPTOR IN BREAST CARCINOMA USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

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Lab Invest; 46(1):60A 1982

Indirect demonstration of estrogen receptor protein (estrophilin) by immunocytochemical staining for estrogen, following incubation of tissue sections with estradiol, has been reported in recent years, but serious questions remain concerning the specificity and sensitivity of these techniques. As a logical follow-up to the preparation of monoclonal antibodies to estrophilin, we investigated the possibility of directly detecting estrogen receptor in breast tissue with these antibodies. Four-micrometer thick sections from 43 mammary carcinomas were stained with peroxidase-antiperoxidase technique using two different monoclonal antibodies to estrophilin. Paraffin sections of MCF-7 cell line were used as positive controls, and antibody controls consisted of adjacent sections treated with estrophilin-absorbed antibody or with monoclonal antibody to calf estrogen receptor. Positive reaction occurred in the cytoplasm and occasionally in the nuclei of 18 mammary carcinomas. Although considerable heterogeneity in intensity of stain existed among the cells in positive tumors, there was a good correlation between the biochemical determination of estrogen and immunohistologic reaction for estrophilin. (no Refs)

28. EFFECT OF MONOCLONAL ANTI-TYROSINE HYDROXYLASE ANTIBODIES ON MELANOMA CELL DIFFERENTIATION (MEETING ABSTRACT)

Hakim AA, Joseph CE
University of Illinois at the Medical Center, Chicago, IL
Hybridoma; 1(2):195 1982

Tyrosine hydroxylase (TH) is a key enzyme in melanogenesis. The present studies examined the biological effects of Hy' on melanotic melanoma cell lines. Three melanoma cell lines were examined for responsiveness to estrogen, binding of estradiol, TH-activities and melanin biosynthesis. Aliquots of each were cultured in parallel in (A) DMEM (Dulbecco's minimum essential medium), and (B) DMEM supplemented with the monoclonal anti-tyrosine hydroylase Hy-7'. Both cultures were incubated in the same incubator with 5% CO2 humidified sterile air, fed at the same time and with the same volume of their nutrients, and they were split at the same time and at the same proportion. Both cell cultures maintained approximately the same doubling time. The (A)-cultures remained melanotic and responsive to estrogen. Their cytosols maintained estradiol-binding affinity. The (B) cultures became amelanotic, non-responsive to estrogens and their cytosols did not bind estradiol, and had statistically non-significant tyrosine hydroxylase activity. Scatchard analysis of estradiol binding of cytosols from cultures of mammary epithelial (ME), mammary carcinoma (mCa) and malignant melanotic melanoma (MMM) cells showed that Hy-7' inhibited estrogen binding to cytosols from (MMM) cells. Hy-7' had no effect on estrogen binding to cytosols of either EM or mCa cells. Hy-7' antibodies inhibited melanin synthesis in MMM cells. It had no effect on melanin synthesis in normal pigmented epithelial cells. (1 Ref)

29. CORRELATION OF ESTROGEN BINDING BY HISTOCHEMISTRY IN BREAST CANCER WITH CLINICAL RESPONSE TO HORMONAL THERAPIES (MEETING ABSTRACT)

Pertschuk LP, Eisenberg KB, Leo VC, Carter AC, Gaetjens E
Department of Pathology, Downstate Medical Center, State University of New York, Brooklyn, NY
Lab Invest; 46(1):65A 1982

Estrogen binding studies were performed by histochemistry in 117 cases of stage IV breast cancer. The ligand employed was fluorescein-labeled bovine serum albumin-estradiol, with estradiol covalently linked at position 17 via a hemisuccinate bridge. Competitive binding studies with a 100-fold excess molar concentration of nitromifene citrate (CI-628; 10-5M) were run in parallel. The findings were then semiquantified to reflect the ratio of tumor cells to stroma, percentages of positively stained cells, and intensities of fluorescence. The tumors were then divided into three categories: zero to trace, low to intermediate, and high to very high, to reflect the degrees of ligand-conjugate binding, and results correlated with clinical response to various hormonal therapies. A zero to trace computation correlated with a failure to respond in 41 of 44 cases (93 per cent), low to intermediate levels correlated with a favorable response in 11 of 36 patients (31 per cent), whereas high to very high levels correlated with a mixed, partial, or complete clinical response in 17 of 26 women (65 per cent). Nuclear binding was a major morphologic feature in 11 additional cases. In this latter group, only three cases showed a successful therapeutic response (27 per cent). Although the histochemical technique may be identifying steroid-binding elements other than the type I estrogen receptor, these results indicate that the method may be of significant value in predicting clinical hormone responsiveness. (no Refs)

30. IMMUNOHISTOCHEMICAL DETECTION OF ESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS USING ANTIRECEPTOR ANTIBODIES: ITS APPLICATION TO CYTOLOGIC MATERIAL (MEETING ABSTRACT)

Tamura H, Raam S, Nemeth E, Cohen J
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Lab Invest; 46(1):82A 1982

The dextran-coated charcoal (DCC) method measures exclusively estrogen-unoccupied receptors and is most widely used for measuring estrogen receptors (ERP) in breast carcinomas (CA). An indirect immunofluorescent technique (IF) utilizing rabbit antiserum raised against ERP of human breast cancer, cytosols has been developed in our lab and their specificity to ERP (unoccupied or occupied by estradiol) confirmed by both biochemical and immunochemical parameters. When the IF method was applied to frozen sections of breast CA, results of the presence/absence of ERP showed a high correlation with DCC results. In this report the results of an IF method when applied to cytologic material are discussed. In 11 breast CA cases thin needle aspiration smears were prepared from fresh biopsy tissue or mastectomy specimens. In one case cell smears were prepared from cytologically positive pleural fluid from a breast CA patient. Whenever possible a parallel experiment was conducted using the cryostat sections, ERP assessed by IF method and the results compared with those of DCC assay. Five of five cases of ERP-rich tumors showed 2 to 3+ cytoplasmic fluorescence. ERP+ tumors with DCC values of 12, 21, and 42 fmoles per mg showed 1 to 2+ staining in the cytoplasm. One tumor from a premenopausal woman measured 12 fmoles per mg of ERP by DCC assay, but IF showed 3+ staining suggesting the presence of an estrogen-occupied stage of ERP. Two cases were ERP (-) by both DCC and IF methods. (no Refs)

31. HORMONE RECEPTOR STATUS OF BREAST CARCINOMA (MEETING ABSTRACT)

Schwarz M
No affiliation given
Breast Cancer Symposium, May 29-30, 1981, Melbourne, Australia Monash University; 1981

Estrogen and progesterone receptors are a major index of the biological aggressiveness of breast carcinomas. They appear to be a major independent prognostic variable for disease recurrence and overall survival and provide the best currently available objective critera for the selection of patients likely to respond to endocrine manipulation. The hormone receptor status of the primary breast carcinoma seems highly representative of that of the tumor tissue at the time of initial dissection. The incidence and concentration of estrogen receptors tends to increase with patient age. Patients with negative estrogen receptor tumors have a less than 10% chance of responding to hormonal manipulation. Estrogen receptor positive tumors still only have a 50-60% chance of responding to endocrine manipulation, suggesting qualitative as well as quantitative interactions, in the estrogen receptor complexing sequence. The qualitative level of estrogen receptor and the concomitant presence of progesterone receptors is a true indication of a highly favorable response to endocrine manipulation. The role of androgen and glucocorticoid receptors is still speculative. The measurement of estrogen and progesterone receptor status of breast carcinoma should be routinely performed if logistically possible. (no Refs)

32. TAMOXIFEN TREATMENT FAILURES IN HORMONALLY RESPONSIVE BREAST CANCERS: CORRELATION WITH STEROID HORMONE RECEPTORS (MEETING ABSTRACT)

Bloom ND, Fishman JH
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Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

An investigation was conducted to determine if receptor sensitivity to Tamoxifen might be involved in lack of response to this agent of some tumors which might otherwise be expected to be hormonally responsive. Clinical correlation of treatment response with estrogen and progresterone receptors in 81 patients revealed a response rate of 76% if both receptors were present in the tumor. The response rate was 89% in those patients with positive receptors in whom an endocrine ablative procedure was performed and was 63% in those patients treated with Tamoxifen. These findings suggested that the later modality may not be effective in the treatment of some hormonally responsive tumors. An assay to determine receptor sensitivity to Tamoxifen was developed and correlated with the clinical response to Tamoxifen treatment in 19 receptor positive patients. Seven patients failed to respond to treatment and in all of these patients their tumors demonstrated insensitivity in vitro to the Tamoxifen molecule. Two patients were subsequently treated with aminoglutethimide and responded. These studies suggest that the failure to respond to Tamoxifen in receptor positive tumors is due to an inability of the receptor to accept the Tamoxifen molecule and not a reflection of hormonal insensitivity. (no Refs)

33. CORRELATION OF ESTROGEN RECEPTOR LEVELS WITH DNA-DEPENDENT RNA POLYMERASE ACTIVITY IN 7,12-DIMETHYL BENZ(A)ANTHRACENE (DMBA)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT)

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Med Pediatr Oncol; 10(1):101 1982

Approximately 60% of breast cancer patients have estrogen receptors (ER) of which two thirds respond favorably to hormonal therapy. Estrogens act on their target tissues by interacting with their cytoplasmic receptors, followed by translocation of the estrogen receptor complex into the nucleus. This results in increased RNA synthesis as evidenced by increased RNA polymerase activity. Using DMBA-induced mammary tumors in rats, experiments were designed to see whether RNA polymerase activity of isolated tumor nuclei may be related to their cytoplasmic ER levels. Mammary tumors were induced by a single intragastric feeding of 15 mg DMBA in 1.5 ml peanut oil. Mammary tumors were analyzed for ER using dextran coated charcoal or sucrose density gradient methods. Tumor nuclei were isolated using fresh, minced tissue and analyzed for RNA polymerase activity as previously described. Seventyseven percent (10/13) of ER positive greater than 10 femto moles/mg protein) tumors exhibited low RNA polymerase activity (less than 200 pico moles of 3H-UMP/mg DNA). In contrast 83% (5/6) of ER negative (less than 10 femto moles/mg protein) tumors showed high RNA polymerase activity (greater than 200 pico moles of 3H-UMP/mg DNA). Similarly, the incorporation of 3H-AMP into RNA was lower (less than 200 pico moles/mg DNA) in 91% (10/11) of ER positive tumors, whereas the majority of ER negative tumors (63%) showed higher (greater than 200 pico moles/mg DNA) 3H-AMP incorporation. The incorporation of 3H-GMP into RNA also exhibited a similar correlation to ER. These data suggest additional biochemical parameters to distinguish between ER positive and ER negative tumors. (1 Ref)

34. CORRELATIONS BETWEEN HISTOLOGICAL PROGNOSTIC FACTORS AND ESTROGEN RECEPTOR LEVELS IN PRIMARY BREAST CANCER.

Pratola D, Verhest A
Service d'Anatomie Pathologique, Cliniques Universitaires de Bruxelles, Hopital Erasme, Brussels, Belgium
Rev Med Brux; 3(3):143-146 1982

The prognostic value of histological grade, histological type, and levels of estrogen receptors (ER) and the correlation among the factors were studied retrospectively for 490 breast cancer (BC) patients. Parameters considered in relation to histological grading included the tendency to form glandular cavities, the number of hyperchromatic and mitotic nuclei, and the degree of nuclear anaplasia. Of the 490 BC, 342 were invasive with 89/342 Grade I, 133/342 Grade II, and 120/342 Grade III. Another 106 cases were classified as special forms of BC, and the remaining 42 cases were excluded due to premastectomy radiotherapy or due to technical reasons. The results confirmed the prognostic value of histological grade. Recurrence-free 5-yr survival was reported for 75% of BC patients with Grade I tumors, 55% of those with Grade II, and 45% of those with Grade III. Five-yr survival rates for patients with grade I-III tumors were 85%, 68%, and 45%, respectively. Histological grade and the level of ER showed a strong negative correlation: 91.8%, 80.6%, and 61.5% of Grade I-III tumors, respectively, were ER-positive. Elevated levels of ER were found in patients with cribriform (92.9%) and lobular (90.9%) tumors. The presence of ER was of no prognostic value in relation to survival and disease-free interval. (18 Refs) (In FRE)

35. BIOCHEMICAL ASSESSMENT OF HISTOCHEMICAL METHODS FOR OESTROGEN RECEPTOR LOCALISATION.

Underwood JC, Sher E, Reed M, Eisman JA, Martin TJ
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J Clin Pathol; 35(4):401-406 1982

The biochemical validity of published labeled-ligand and ligand-antibody methods for the histological localization of estrogen receptors (ER) in breast carcinomas was assessed by measuring specific and non-specific binding of 3H-estradiol to pretreated MCF-7 monolayers; the monolayers had been either frozen and thawed, then air-dried or acetone-fixed, or fixed in formaldehyde to reproduce the conditions in published methods. The results indicate that most of the ER in a frozen section is likely to be lost by diffusion into the supernatant incubation medium. Fixation substantially restricts diffusion but reduces specific estradiol binding and may increase non-specific binding; acetone fixation is particularly deleterious. Preincubation in estradiol fails to protect the receptor during fixation. We conclude that the published histochemical methods for ER localization have doubtful validity and should not yet be used in preference to conventional biochemical assays. (Author abstract) (22 Refs)

36. GLUCOCORTICOID RECEPTORS, CLINICAL CHARACTERISTICS, AND IMPLICATIONS FOR PROGNOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Simonsson B, Terenius L, Nilsson K
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Cancer; 49(12):2493-2496 1982

The cytoplasmic glucocorticoid-receptor (GR) content was analyzed in peripheral leukocytes from 52 nonselected patients with chronic lymphocytic leukemia (CLL). Forty-six patients had measurable GR levels. Six patients lacking measurable GR and seven of eight patients with a low GR content had inactive disease. However, there was no significant difference in average GR content between patients with progressive or nonprogressive disease. Twelve GR-positive patients were treated with prednisolone as the sole medication. Seven patients responded, some in several treatment sessions. There was no correlation between GR-content and clinical response. Thus, in our experience, cytoplasmic GR measurement has only limited predictive value. (Author abstract) (11 Refs)

37. RELATIONSHIPS BETWEEN STEROID RECEPTOR AND EPITHELIAL CELL PROLIFERATION IN BENIGN FIBROCYSTIC DISEASE OF THE BREAST.

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Cancer; 49(12):2534-2536 1982

Tissue specimens from 27 patients with mammary fibrocystic disease were assayed for estrogen (ER) and progestin (PR) receptors. Seventeen patients (63%) had ER-positive lesions (greater than 5 fmol/mg protein). A progression in ER presence was noted from fibrocystic disease (33%) and fibrosing adenosis (50%) to lobular and ductal hyperplasia (85%). Similarly, ER content increased from 14.5 +-13 fmol/mg cytosol protein in fibrocystic disease and fibrosing adenosis to 31.5 +-23 fmol/mg protein in epithelial hyperplastic lesions. Furthermore, the ER-PR couple was only encountered in lobular and ductal hyperplasia. The authors' data indicate that the incidence of steroid receptor parallels the intensity of hyperplasia in benign breast disease. (Author abstract) (15 Refs)

38. A MICRO-ASSAY FOR ESTROGEN RECEPTOR IN BREAST TUMOR WITH USE OF 125I-LABELED ESTRADIOL.

Van NT, Fritsche HA, Trujillo JM
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Clin Chem; 28(6):1303-1308 1982

The concentration of estrogen receptor protein in breast-tumor tissue is generally expressed in units of femtomoles of estradiol bound by the receptor per milligram of cytosol protein. The sensitivity of the estrogen receptor radioligand assay is therefore related to the specific activity of the steroid label used for the binding assay, the amount of the receptor protein in the vol of cytosol used, and the protein concentration in the cytosol. In this paper, we discuss factors affecting the sensitivity of the estrogen receptor assay and present various approaches for optimizing the assay. We also describe a procedure that involves a radioiodinated estradiol of high specific activity, a micro-technique for preparing tumor cytosol, and a micro-assay procedure with which the estrogen receptor protein can be measured in as little as 50 mg (wet weight) of tissue. (Author abstract) (7 Refs)

39. SPECIFIC CYTOTOXICITY OF 16ALPHA-[125I]IODOESTRADIOL FOR ESTROGEN RECEPTOR-CONTAINING BREAST CANCER CELLS.

Bronzert DA, Hochberg RB, Lippman ME
Medicine Branch, NCI, Bethesda, MD, 20205
Endocrinology; 110(6):2177-2182 1982

We attempted to induce specific killing of estrogen receptor-containing breast cancer cells using estradiol coupled to a high specific activity gamma emitting isotope of iodine. MCF-7 human breast cancer cells were incubated with 16alpha-[125I]iodoestrodiol alone ([125I]E2), or with 16alpha-[125I]iodoestradiol plus 100-fold excess 17beta-estradiol (E2), and then viably frozen. After 8 wk, the [125I]E2 exposed cells and the [125I]E2 plus E2 exposed cells were 10% and 77% of controls, respectively. When the breast cancer cell line MDA-MB-231 which does not contain estrogen receptors was used, the rate of cell death was similar to the competed MCF-7 cells. When specific cytotoxicity was compared using a cloning technique, nearly a 5 log reduction in surviving cell fraction was seen with [125I]E2, as compared to identical cells treated with [125I]E2 plus competitor. This technique shows promise for selecting a population of cells with defects in their estrogen receptor and in studying subcellular hormone interactions. (Author abstract) (9 Refs)

40. PROGESTIN RECEPTORS IN PROLACTIN AND GROWTH HORMONE PRODUCING TUMOURS IN RATS.

Naess O, Haug E, Attramadal A, Gautvik KM
Inst. Pathology, Rikshospitalet, Oslo, Norway
Acta Endocrinol (Copenh); 100(1):25-30 1982

Progesterone and corticosterone have a similar effect on the production of growth hormone (GH) and prolactin (Prl) by pituitary tumor cells (GH3 cells) in culture. Previously we have shown that progesterone had a high affinity for the glucocorticoid receptors in these cells. Progesterone may therefore exert its effects through binding to the glucocorticoid receptor. The aim of the present study was to investigate if the GH3 tumor cells and an estrogen induced pituitary tumor, which also produce GH and Prl, possess specific receptors for progesterone. Both the GH3 tumors and the estrogen induced pituitary tumor were in fact found to possess cytoplasmatic receptor molecules for progesterone by using the potent progestin R5020 as a marker. Isoelectric focusing revealed one binding component (pH 5.9), which was of protein nature. The binding was of high affinity (KD 2 x 10(-9) mol/l). In the estrogen induced tumor, the maximal binding was 70 fmol/mg cytosol protein. In female rates with GH3 tumors the binding was 55 fmol/mg cytosol protein. Priming of the animals with 1 mg estradiol-valerate increased the binding to 116 fmol/mg cytosol protein, whereas very little binding was found in GH3 tumors from rats castrated 7 days before sacrifice. The receptors in the estrogen induced pituitary tumor and the GH3 tumors exhibited high affinity for R5020 and progesterone, whereas corticosterone had no significant affinity for the receptors. Using exchange assay, it was demonstrated that the cytoplasmic progestin receptors could be translocated to the nucleus after administration of progesterone to the animals. Thus, the presence of specific progesterone receptors, different from the glucocorticoid receptors, strongly indicates that the effects of progesterone on GH and Prl production are mediated through the progesterone receptors. (Author abstract) (21 Refs)

41. ESTROGEN RECEPTORS IN PRIMARY BREAST CANCER.

Neifeld JP, Lawrence W, Brown PW, Banks WL, Terz JJ
Medical Coll. Virginia, Virginia Commonwealth Univ., Box 11, MCV Station, Richmond, VA, 23298
Arch Surg; 117(6):753-757 1982

Estrogen receptor (ER) activity was assayed in 132 patients undergoing mastectomy for primary breast cancer and in 75 patients whose initial treatment for metastatic cancer was endocrine manipulation. Estrogen receptor status correlated with response to endocrine therapy. Among patients whose ER activity was assayed in the primary tumor, ER-positive patients had an improved disease-free survival (independent of stage or nodal or menopausal status) after mastectomy when compared with ER-negative patients (p less than 0.05). The ER-positive and ER-negative patients receiving adjuvant chemotherapy had similar disease-free survivals. These data confirm that patients with ER-positive primary tumors have a better prognosis than patients with ER-negative primary tumors. Although adjuvant chemotherapy improves the prognosis in patients with histologically positive lymph nodes in both ER-positive and ER-negative patients, the disease-free survivals in ER-negative patients may improve to a greater extent than in ER-positive patients. (Author abstract) (15 Refs)

42. THE CLINICAL APPLICATION OF OESTROGEN RECEPTOR ANALYSIS IN EARLY CANCER OF THE BREAST.

Cooke T
Faculty of Medicine, Univ. Southampton, Southampton, England
Ann R Coll Surg Engl; 64(3):165-170 1982

The analysis of receptors for estrogen in early cancer of the breast may be used to predict prognosis. The presence or absence of estrogen receptors is independent of menstrual status, the stage of the patient's disease, and the histological grade of the tumor. Therefore combination with other prognostic factors gives a more accurate assessment of an individual patient's outlook. In the study described prognostic subgroups were determined from tumor axillary lymph node histology and estrogen receptor status. The clinical application of these findings is discussed. (Author abstract) (3 Refs)

43. TAMOXIFEN THERAPY IN ADVANCED BREAST CANCER WITH POSITIVE ESTROGEN RECEPTORS IN POSTMENOPAUSAL WOMEN.

Bono A, Fariselli G, Bettoni I, Alloisio M, Nicoli N, Di Pietro S
Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy
Tumori; 68(2):143-147 1982

Sixty-five postmenopausal patients with metastatic or surgically unresectable primary breast cancer, all estrogen receptor (ER) positive, were treated with tamoxifen 20-40 mg a day. Overall objective response rate was 58%, with median duration time of 13 mo. The correlation between response rate and ER levels appears positive, although not statistically significant. The analysis of the data was also performed in the subgroups 'locally advanced tumors' and 'recurrences and metastases'. (Author abstract) (9 Refs)

44. CYCLIC AMP BINDING PROTEINS, OESTROGEN RECEPTORS AND PROGESTERONE RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT)

Watson D, Hawkins RA, Senbanjo R, Telford J, Forrest AP
Department of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland, Miller, W. R.
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

While human breast cancer which possess estrogen receptor (ER) and progesterone receptor (PgR) activities are likely to be hormone responsive, many do not respond to endocrine therapy. In hormone-dependent rat mammary tumors the ratio of cyclic AMP binding proteins to steroid receptors may better discriminate hormone dependent from independent tumors than steroid receptors alone. The inter-relationships between cyclic AMP binding protein, ER and PgR activities have therefore been determined in 100 human cancers. Cyclic AMP binding was detected in all tumors, ER in 70 and PgR in 38. Mean cyclic AMP binding level in ER negative tumors was significantly higher than in the ER positive group. In tumors with both activities there was no significant correlation between levels of binding. Similar relationships were also found between cyclic AMP binding and PgR. Expressing results as ratios of ER to cyclic AMP binding proteins neither divided the tumors into obvious subgroups nor discriminated between PgR positive and negative tumors. (no Refs)

45. THE TECHNIQUE AND POTENTIAL APPLICATION OF PROGESTERONE RECEPTOR MEASUREMENT BY ISOELECTRIC FOCUSING (MEETING ABSTRACT)

Harland R, Hayward E, Barnes DM, Howell A, Skinner LG, Sellwood RA
Department of Surgery, Withington Hospital, Manchester, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Recently the induction of progesterone receptor (RPc) synthesis in human breast cancer by tamoxifen has been described and it has been suggested that this may give a specific prediction of hormone response. However, metastases may be inaccessible or too small for assay by standard techniques (Scatchard analysis). This reduces the value of any test which relies on RPc measurement at the time of treatment. A method has been developed which allows the use of small samples including needle biopsies for RPc estimation. After incubation of cytosol (minimum total volume 70ul) with tritiated R5020 (a synthetic progestagen), hormone-labelled receptor was separated by iso-electric focusing (IEF). RPc measured by IEF, although an underestimate, correlates with Scatchard analysis (rho equals 0.89) with a specificity of 94% and a lower limit of sensitivity of 30 fmol/ml cytosol. This method has allowed us to measure RPc before and after starting tamoxifen in 14 patients of whom 4 showed induction of RPc. Progression of disease by 3 and 6 months respectively was seen in 0/4 and 0/3 patients in whom RPc was induced compared with 6/10 and 7/7 patients in whom no induction occurred. RPc assay by IEF increases the availability of RPc data in metastatic disease and may allow an early indication of hormone response. (1 Ref)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

46. EFFECT OF PROGESTINS ON ULTRASTRUCTURE OF ENDOMETRIAL CELLS IN PRECANCEROUS CONDITIONS AND CANCER OF THE ENDOMETRIUM (ANALYSIS OF THE ORGAN CULTURE).

Belineva LA, Bukhvalov IB, Zheleznov BI, Raikhlin NT
Lab. Pathology, All-Union Res. Center Motherhood and Childhood Protection, Moscow, USSR
Arkh Patol; 44(4):18-25 1982

The efficacy of progesterone (PG) and its synthetic analog norethisterone (NS) was studied in organ cultures of endometrium obtained at diagnostic curettage from the women with precancerous conditions or cancer of the endometrium. The cultures were incubated with PG or NS. After 72-hr incubation, the endometrium specimens were subjected to electron microscope examination. Ultrastructural characteristics of cultured cells of atypical hyperplasia, focal adenomatosis, and endometrial adenocarcinoma included an increase of the fraction of diffuse chromatin, dilatation of the cisterns of the endoplasmic reticulum, enlargement of mitochondria, and appearance of cytoplasmic filaments. Incubation with PG and NS resulted in the reduction in the number of microvilli, marked increase in the number of microfilaments, and appearance of giant mitochondria. These findings indicate that the endometrial cells in atypical hyperplasia, focal adenomatosis, and endometrial adenocarcinoma retain the specific receptor system which controls interaction of steroid hormones and cells of target organs. (16 Refs) (In RUS)

47. ENDOCERVICAL CHANGES IN THE GUINEA PIG AFTER TREATMENT WITH 17-BETA-OESTRADIOL AND 9,10 DIMETHYLBENZANTHRACENE.

Thomas JA, Dallenbach FD
Dept. Pathology, St. John's Medical Coll., Bangalore 560 034, India
Adv Exp Med Biol; 144:281-284 1982

The possible synergistic effect of exogenous estrogen (17-beta-estradiol) and 9,10-dimethylbenzanthracene on guinea pig endocervices was investigated. Electron microscopy showed membrane thickening, mild dysplasia, and mucus cell differentiation and combined mucus and squamous cell differentiation. The well differentiated mucus cells contained excessive amounts of mucus; the little mucus released was by mucus-globus extrusion or release of partially or wholly membrane-bound mucus globule packets. (2 Refs)

48. EFFECT OF HYDROCORTISONE ON COLONY-FORMATION AND DIFFERENTIATION OF HEMATOPOIETIC STEM CELLS (CFUS) IN INTACT AND IRRADIATED MICE.

Shvets VN
No affiliation given
Radiobiologiia; 22(2):264-268 1982

Effect of hydrocortisone (HC) on hematopoietic stem cells was studied in (CBA x C57Bl)F1 mice. The irradiated (1,000 rads) recipients were inoculated iv with syngeneic spleen or bone marrow cells preincubated with HC (in vitro experiment). In in vivo experiment, HC was inoculated within different time periods after transplantation of bone marrow cells. In vitro incubation with HC did not affect the number and differentiation of colony-forming units (CFU) in the spleen and bone marrow. In vivo HC administration produced marked decrease of granulocytic and megakaryocytic colonies. (10 Refs) (In RUS)

49. MONOOXYGENASE AND EPOXIDE HYDROLASE REGULATION IN PRIMARY FETAL RAT LIVER CELL CULTURE.

Gielen JE, De Graeve J, Goujon F, Kremers P, Van Cantfort J
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Adv Exp Med Biol; 136(partA):87-98 1982

Presence of cytochrome P450 (CP450) was studied in fetal hepatocyte culture and measurements of aryl hydrocarbon hydrolase (AHH), ethoxycoumarin deethylase, aldrin epoxydase, and epoxide hydrolase (EH) activities were measured. The level of CP450 content in primary fetal liver cell culture was stable and did not significantly differ from that found in fetal liver used for the culture preparation. High concentration of phenobarbital (PB) induced both AHH and EH activities, whereas benz(a)anthracene acted preferentially , and 2,3,7,8-tetrachlordibenzo-p-dioxin selectively on AHH activity. AHH and EH activities were modified by addition of dexamethasone. The enzyme activities were first inhibited and then induced when the corticoid concentration was raised from 10(-10) to 10(-4) M. The same shift in the AHH inhibition in vitro by alpha-naphtoflavone (ANF) and metyrapone (MTR) was observed, whether the dexamethasone treatment was carried out in the presence or in the absence of serum. The action of other hormonal steroids on both AHH and EH activities was also studied. The same effect was observed with hydrocortisone; a shift in sensitivity of the control and PB-induced AHH activity in vitro from ANF to MTR, and a fall in the control and PB-induced EH activity. Sex hormones, testosterone (TS) and estradiol (ED) slightly induced the AHH activity and decreased the extent of AHH and EH induction by PB. TS and ED did not decrease the EH activity and did not shift in vitro the sensitivity of either the control or the PB-induced AHH to the inhibitors. According to these observations, glucocorticoids are some of the physiological stimuli controlling the expression of drug metabolizing enzyme activities in the perinatal period of life. (21 Refs)

50. EFFECTS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE ON THYMUS CORTEX IN THE RAT. A MORPHOLOGICAL AND HISTOMETRICAL ANALYSIS.

Tosi P, Luzi P, Miracco C, Del Vecchio MT, Vindigni C
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Virchows Arch [Cell Pathol]; 39(2):125-136 1982

In the rat, administration of 7,12-dimethylbenz(a)anthracene (DMBA) causes necrosis of the inner layers of the adrenal cortex and provokes rising levels of plasma cortisol. Histological and ultrastructural study of the thymus demonstrates a profound depletion of small thymocytes, especially in the inner cortex where they normally represent the greater part of the cell population. The thymic weight, and the cortico-medullary ratio as measured by histometry, decrease significantly. These findings are similar to those observed following steroid administration. However, whereas after steroid treatment restitution of the normal complement of thymocytes occurs within 7-10 days, in the present model the thymic weight and cortico-medullary ratio remain at the low levels observed on Days 1 and 3 until after Day 24 following DMBA administration. A block in the regenerative process is confirmed by the results of morphometrical analysis of the thymocyte nuclear area in the cortex. On Day 1 and 3 after DMBA the mean thymocyte nuclear area is reduced in the outer cortex and increased in the inner cortex, because of the selective destruction of small thymocytes and the migration of the corticoresistant blast thymocytes towards the medulla. Subsequently, until after Day 24 the mean nuclear area of the thymocytes is significantly higher in the outer and in the inner cortex of treated rats than in the corresponding parts of the cortex of control rats. This aspect of the cortex is characteristic of the early phase of the regenerative process, ie of Day 2 or 3 after steroids administration. It can be assumed that in this experimental mode the thymic changes are due not only to the raised cortisol level but also to a direct effect of DMBA on the thymus, which is probably an inhibition of DNA synthesis in cells in the S phase of the mitotic cycle, ie in the replication of DNA. It also seems possible that a causal relationship exists between inhibition of DNA synthesis in proliferating organs like the thymus, and the carcinogenic activity of DMBA. (Author abstract) (35 Refs)

51. ANDROGEN REGULATION OF DMN-N-DEMETHYLASE ACTIVITY IN KIDNEY OF BALB/C MICE (MEETING ABSTRACT)

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Department of Oncology, Howard University College of Medicine, Washington, DC, 20060

Med Pediatr Oncol; 10(1):102 1982

Androgenic hormones have been shown to regulate the biotransformation of Dimethylnitrosamine (DMN) to its active mutagenic metabolite. This androgenic regulation in renal tissue is a receptor mediated phenomenon as androgens are not able to stimulate kidney microsomal enzymes required for Ames test, in Tfm mice. Further, even though hepatic emzymes are more active than the kidney enzymes, the androgen effect is tissue (kidney) specific. Recent observation indicates that this androgenic effect is observed only under conditions when androgen receptors are translocated in the nucleus. The present experiments were designed to test correlations between the mutagenic ability of renal tissue and its N-demethylase activity (an enzyme implicated in conversion of DMN to its active metabolite). N-demethylase activity was measured from micromosomal fractions of liver and kidney (by quantitating formaldehyde formation) according to Nash. The results indicate: (1) higher DMN-N-demethylase activity in liver (male or female, adults) compared to kidney (male or female); (2) higher enzyme activity in adult male compared to adult female renal tissue; (3) complete loss of renal but not liver enzyme activity in mice castrated for 7 days (testosterone treatment, 2 mg/day/10 days, can significantly increase enzyme activity of kidney tissues in such castrates); and (4) a significant increase in DMN-N-demethylase activity in renal tissue of testosterone treated adult female mice. These data indicate androgenic regulation in kidney DMN-N-demethylase activity. The BALB/c mouse kidney system is a useful model to study the mechanism(s) by which steroid hormones augment or inhibit biotransformation of procarcinogens to mutagens which may ultimately lead to tumorigenesis. (2 Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

52. CAFFEINE AND UNSATURATED FAT DIET SIGNIFICANTLY PROMOTES DMBA-INDUCED BREAST CANCER (MEETING ABSTRACT)

Minton JP, Foecking MK, Abou-Issa H
Ohio State University College of Medicine, Columbus, OH
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Caffeine is an important causative agent in the development of human fibrocystic breast and disease. The epithelial proliferation resulting from caffeine consumption has been shown to be reversible when caffeine abstention is carried out. The exposure of a well-established animal model to the known carcinogen dimethylbenz(a)anthracene (DMBA) is associated with the development of a hormone sensitive estrogen receptor positive breast tumor in nearly 90% of the animals. To determine the possibility of caffeine being an extraordinary promoter of breast cancer development in animals consuming vegetable fat the following study was carried out. A controlled study comparing the time to tumor development and the number of tumors and the growth rate of breast cancer in Sprague-Dawley rats which had been given 50 mg of DMBA at 6 weeks of age compared the tumor promotional effects of caffeine alone, caffeine and unsaturated fatty acids in combination, unsaturated fatty acids alone, and a standard rat chow diet. Twenty rats were in each group. The results show that the rat which consumed caffeine and unsaturated fatty acids had the earliest development of tumor, the most multiple tumor occurrence, and the most rapid rate of growth. Average time to development was 94 days. The fat and water rats had an average time of development of 133 and 140 days respectively. The caffeine alone rats had a mean time to tumor development of 188 days. The combination of an unsaturated fat diet and caffeine significantly shortened the time to tumor development when compared with the other three groups. (no Refs)

53. HORMONE RECEPTORS IN COLON CANCER.

Zannini G, Contieri E
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Minerva Med; 73(18):1221-1224 1982

The hypothesis on the presence of specific hormone receptors in neoplasms of the colon was tested in 12 patients with primary multiple malignant tumors and on the effectiveness of adjuvant hormone therapy of 20 patients with inoperable malignant tumors of the digestive tract. Three of the 12 patients with primary multiple tumors had synchronous tumors, and the 9 others had metachronous tumors. Two of the three patients with synchronous tumors had adenocarcinomas of the colon and rectum, respectively, the third had carcinomas. In the nine patients with diachronous tumors the first tumors were located in the breast, larynx, uterus, ovary, thyroid gland and stomach, and the second tumors in the breast, colon, rectum, and sigmoid colon. The group of 20 patients (10 men and 10 women) with inoperable tumors were randomized into two groups. One group was (Group I) subjected to cyclic polychemotherapy, the other (Group II) to cyclic polychemotherapy with medroxyprogesterone acetate (MPA: 1,000 mg/day po). The evaluation after 12 mo showed an improvement concerning anorexia in 20% of the patients in Group I and in 70% in II, concerning dysphagia in 20% and 40%, concerning emesis in 10% and

40%, concerning asthenia in 20% and 70%, concerning pain in 20% and 60%, and concerning ability to work in 20% and 60%, respectively. The 1-yr survival rate were 30% in Group I and 70% in Group II. The findings indicate the effectiveness of adjuvant MPA therapy. (10 Refs) (In ITA)

54. SELENIUM, ESTRADIOL 17BETA, NITRITES, AND HUMAN BREAST CANCER.

Lombard LF
11145 Northborough Lane, Richmond, VA, 23235
Med Hypotheses; 8(4):371-382 1982

An hypothesis postulating an etiology of breast cancer from interactions among selenium, estradiol 17beta, nitrites, and RBC is presented. In this hypothesis, in the presence of nitrites, triglycerides, and selenium, estradiol 17beta is catalyzed by an unknown enzyme (' X') to form the known carcinogen chrysene, which is complexed with methemoglobin in the RBC. The conversion process may partially take place in the gastrointestinal tract and liver, with more direct conversion in breast cells after transport. Chrysene, in the breast cells, already under attack by nitrites or lysosomal enzymes, causes additional focal hyperplasia, metaplasia, neoplasia, anaplasia, gene alteration, and carcinoma. The process may also require high androgen levels and other trace elements, such as zinc. (51 Refs)

55. ANTI-TUMOUR STUDIES ON A NITROSOCARBAMATE OF 19-NORTESTOSTERONE: IN VITRO AND IN VIVO.

Hartley-Asp B, Shepherd R, Stamvik A
AB Leo-Fack, S-25100 Helsinborg, Sweden
INSERM Symp; 19:105-112 1981

The nitrosochloroethylcarbamate of 19-nortestosterone (LS-1727) was tested against L1210 leukemia cells, TLX/5 ascites tumor cells and Ehrlich ascites tumor cells in mice in vivo, and on Walker 256 carcinosarcoma in rats. Only the Ehrlich ascites system confirmed significant activity of LS-1727. Dog, rat, and mouse liver homogenate experiments suggested that inactivity could be caused by detoxification of LS-1727 in vivo. (10 Refs)

56. THE EFFECT OF A POTENT LHRH ANALOGUE IN THE TREATMENT OF PROSTATIC CANCER (MEETING ABSTRACT)

Trachtenberg J, Tolis G
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Certain LHRH (luteinizing hormone-releasing hormone) analogues have been shown to markedly reduce gonadal steroidogenesis in a variety of animals. In order to assess to the effect of the chronic administration of a potent LHRH analogue, (D-Ser(But)6)LRH(1-9)-nonapeptide-ethylamide (Hoechst, Hoe766) on prostatic tissue, adult Wistar rats were administered either 1, 3 or 13 ug of Hoe766 sc QD. At 7, 21 and 35 days of treatment, groups of animals were sacrificed and certain serum endocrine and gravimetric parameters determined. By the end of the experimental period neither serum LH nor prolactin was altered from control but serum estradiol, testicular LH receptor content, testicular weight, seminal vesicle weight, and prostate weight were markedly decreased from control; serum androgens were reduced to the castrate level. Hoe766 was also administered to 6 adult males with previously untreated metastatic prostatic cancer. Fifty ug of Hoe766 was administered sc QD or 500 ug intranasally QD for periods from 3 to 6 months. By 3 months of treatment serum prolactin and LH had not changed, but serum androgens and estradiol had declined to the castrate level and LH response to LHRH administration, serum acid phosphatase, and prostatic tumor volume as measured by pelvic ultrasound and bone scan were all markedly reduced. Hoe766 reduces serum androgens to the castrate level in both the rat and man, probably by acting at two sites, namely the pituitary (as evidenced by decreased LH response to LHRH administration) and the testis (as evidenced by decreased testicular LH receptor content). (no Refs)

57. LEUPROLIDE IN METASTATIC PROSTATIC CANCER (MEETING ABSTRACT)

Smith JA
Abbott Leuprolide Prostatic Cancer Study Group, Salt Lake City, UT
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Leuprolide is a new, potent analogue of gonadotropin releasing hormone which with chronic administration results in inhibition of pituitary release of LH and FSH (luteinizing and follicle stimulating hormones). Consequently testicular function is suppressed in men and circulating serum testosterone levels reduced. These observed endocrine effects of Leuprolide have predicated its use in prostatic cancer. One hundred and seventeen patients with metastatic prostatic cancer have been treated with Leuprolide in a multi-center Phase I-II study. Fifty-seven patients had received some form of prior endocrine treatment and 60 had no prior therapy. Patients were followed every two weeks and serial bone scans, x-rays and serum chemistries and hormones obtained according to protocol. Response criteria were those defined by the National Prostatic Cancer Project. Serum testosterone and dihydrotestosterone were suppressed to castrate levels in all patients within four weeks of the initiation of treatment. No adverse reactions or gynecomastia were encountered in any patients although most had hot flashes. Thirty previously untreated patients are evaluable to date and 70% have obtained a complete or partial objective response. An additional 27% have objectively stable disease and most patients had subjective improvement with resolution of bone pain or improvement in performance status. All responding patients are continuing on treatment. Only one patient in the previously untreated category had disease progression at week 10 of treatment. Thirty percent of patients who had relapsed on prior endocrine treatment had some subjective improvement with Leuprolide and 2 achieved an objective response. (no Refs)

58. A UNIFIED CONCEPT FOR THE TREATMENT OF METASTATIC RENAL CELL CARCINOMA (MEETING ABSTRACT)

Pontes JE, Wajsman LZ, Beckley S
No affiliation given
77th Annual Meeting of the American Urological Association, Inc May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The treatment of metastatic renal cell carcinoma is at the present time inadequate because of the lack of effective chemotherapeutic agents. An overall plan of therapy based on the preparation of tumor for immunotherapy, receptor analysis and clonogenic assay was devised in an attempt to improve the results of therapy in this disease. A second line of therapy for patients who failed the above treatment plan consisting of systemic hyperthermia or large doses of chemotherapy with bone marrow autotransplant, has also been initiated. Twenty-seven patients had tumor excised and processed for specific immunotherapy. Twenty patients received at least 2 treatments and 10 received more than 4 treatments. There was one complete and one partial response among patients with multiple metastasis and 2 partial and 2 complete responses among patients with minimal disease. Estrogen receptor analysis was done in 28 specimens and progesterone receptor analysis in 13. Estrogen receptors were present in the specimens of 5 patients evaluated by SDG (4S -3 to 24 fm/mg) and in 2 patients evaluated by DCC method. Progesterone receptors were present in 3 out of 13 patients analyzed. The significance of these findings are not known since these patients are still undergoing other forms of therapy. Clonogenic assay testing was possible in 15 out of 28 patients. Several chemotherapeutic agents were tested including 2 new agents (CHIP cis-dichlorobis(isopropylamine)trans-dihydroxy-platinum IV and DAMP (2,4-diamino-5-(1-adamantyl)-6-methylpyrimidine)). A variable pattern of response was present in each tumor tested. In only one tumor a 100% inhibition of the colonies was found. Two patients have entered a systemic hyperthermia protocol and in one case over 50% decrease of a large scalp lesion was observed. (no Refs)

59. CLINICAL AND BIOCHEMICAL EFFECT OF AMINOGLUTETHIMIDE IN TREATMENT OF ADVANCED PROSTATIC CARCINOMA (MEETING ABSTRACT)

Worgul T, Santen RJH, Samjlik E, Lipton A, Harvey HA, Veldhuis JD, Drago J, Rohner TJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc; May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Treatment for patients with advanced prostatic carcinoma with disease progression after endocrine therapy is generally unsatisfactory. However, some 20 per cent of patients respond to additional antiandrogen therapy, Flutamide, and/or adrenalectomy indicating a continuing hormonal responsiveness. Twenty-five previously castrate patients with stage D prostate carcinoma were treated with aminoglutethimide. One patient has now had a complete response and is in remission after 250 weeks. A partial response was seen in 4 patients (CR + PR equals 20 per cent) and 6 patients were objectively stable. Pretreatment serum testosterone and dihydrotestosterone levels were 27+ or-5 and 10+ or-3 ng/100 ml, respectively and were reduced to 12+ or-2 and 6+ or-1 ng/100 ml during aminoglutethimide therapy. Drug toxicity occurred in some 52 per cent of patients but was transient. These data compare favorably to response rates seen after pituitary ablation surgical adrenalectomy, Flutamide and chemotherapy in end-stage prostatic carcinoma. (no Refs)

60. BIOCHEMICAL AND CYTOKINETIC STUDIES ON CORTICOSTEROID SENSITIVITY OF RIF TUMOURS (MEETING ABSTRACT)

Braunschweiger PG, Schiffer LM
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Cell Tissue Kinet; 15(1):100 1982

Previous studies in C3H/HeJ mammary and Lewis lung tumors indicate that corticosteroid treatments induced a reversible G1 progression delay. The response in these tumors was apparently mediated by specific corticosteroid receptors. In the present studies RIF tumors growing in female C3H/HeJ mice were found to have specific corticosteroid receptors (GR) which bind 3H-dexamethasone (dex) at high affinity and low capacity. The 3H-dex-GR complex was found to bind specifically to isolated RIF nuclei at 23C but not at 4C. In-vitvo treatment with dex showed dose dependent tumor growth inhibition and cytokinetic studies indicated G1 progression delay. The effect of dex on the survival and proliferation (by Hu killing) of the RIF clonogenic cell population will be presented. (no Refs)

61. THE ROLE OF ESTROGENS IN MASTOPATHY AND MAMMARY CANCER IN PERIMENOPAUSAL WOMEN.

Greenblatt RB, Vasquez J, Samaras C, Nezhat C
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30901
J Am Geriatr Soc; 30(3):165-169 1982

Fibrocystic disease of the breast (FCD) is an exaggeration of the normal physiologic response to cyclic estrogen and progesterone stimulation. The disorder can persist, with much less severity, in the menopausal woman. Whether FCD predisposes to mammary cancer remains moot. A new steroidal agent, danazol, can eliminate nodosities in the majority of women with FCD. Thermography may identify women who are at greater risk because of increased heat production. Mammography should be employed in women with persistently abnormal thermograms, even though no suggestive breast masses are palpable. Needle biopsy or surgical biopsy should be undertaken whenever a firm indurated mass is palpated, regardless of negative findings with a thermogram or mammogram. In a series of 1,548 women treated for 10,715 women-years, the incidence of breast cancer after prolonged estrogen therapy was not increased. Although estrogens and prolactin have been incriminated in the etiology of mammary cancer, no hard facts exist to confirm such allegations. (Author abstract) (34 Refs)

62. CAN PRIMARY ENDOMETRIAL CARCINOMA STAGE I BE CURED WITHOUT SURGERY AND RADIATION THERAPY?.

Bokhman IaV, Chepik OF, Volkova AT, Vishnevskii AS
N. N. Petrov Res. Inst. Oncology, USSR Ministry of Health, Leningrad, USSR
Vopr Onkol; 28(3):34-42 1982

Data on 15 cases of primary endometrial carcinoma Stage I (mean age -26.0 yr) cured by administration of hydroxyprogesterone capronate without surgery and radiation therapy are presented. Clinical recovery in II cases was confirmed by repeated cytological and histological examinations of the endometrium. Hydroxyprogesterone-capronate dose per course ranged within 25-83.0 g. In four cases of moderately differentiated adenocarcinoma, hormonal treatment was carried out in combination with chemotherapy. When tumor regression was confirmed histologically steroid contraceptives were administered to induce menstrual cycling artificially. At the closing stage of therapy estrogens and progestagens or clomiphene citrate were given in succession to restore ovulatory cycle. Prospects of administration of progestagens in certain cases among young patients with endometrial carcinoma Stage I as a separate method of therapy are discussed. (Author abstract) (6 Refs) (In RUS)

63. A COMPARISON OF RESULTS OF GESTAGEN THERAPY OF ENDOMETRIAL CARCINOMA WITH THOSE OF PRELIMINARY STUDY OF TUMOR CULTURED CELL SENSITIVITY TO DRUGS.

Schindler C, Pavlovich T
Leipzig, E. Germany
Vopr Onkol; 28(3):52-56 1982

The paper deals with a comparative study on the efficacy of adjuvant gestagen therapy of 61 patients with primary endometrial carcinoma. A control group of 219 patients did not receive hormones. In gestagen group, sensitivity to drugs was determined prior to therapy in 67 cell cultures of carcinoma. This provided a basis for a study of the meaning of a test of sensitivity to drugs which was carried out prior to therapy in order to select a suitable gestagen. Survival (2 yr) was significantly higher in the group in which tumor sensitivity to chosen gestagen was determined in cell culture prior to treatment. Due to selection of suitable gestagen before therapy by means of tumor sensitivity test, a more pronounced clinical effect is obtained. (Author abstract) (19 Refs) (In RUS)

64. INFLUENCE OF CASTRATION AND MOUSE STRAIN ON THE INDUCTION OF PARARENAL ANGIOSARCOMAS AND RENAL ADENOMAS BY 1,2-DIMETHYLHYDRAZINE.

Turusov VS, Chemeris GIu
Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 28(3):82-86 1982

Castration preceding the administration of 1,2-dimethylhydrazine (DMH) to CBA male mice inhibits the induction of pararenal angiosarcomas (from 76% to naught) and renal adenomas (from 89 to 57%). Male mice of different strains treated with DMH developed the following incidences of pararenal angiosarcomas and renal adenomas: C3H -35.5 and 13%, respectively, CBA -97 and 78.8%, (CBA X C57Bl) F1-36.1 and 30%, C57Bl -4.2 and 23.4%, BALB/c -13 and 43.4%, C3HA -7.1 and 14.3%. Pararenal angiosarcoma develops most likely from a vascular bed of renal capsule. The mechanisms of androgen stimulation of renal adenoma and pararenal angiosarcoma induction are discussed. (Author abstract) (11 Refs) (In RUS)

65. OCCURRENCE AND HISTOLOGICAL STRUCTURE OF ADENOCARCINOMA OF THE ENDOCERVIX AFTER LONG-TERM USE OF ORAL CONTRACEPTIVES.

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Frauenklinik im Klinikum Mannheim, Univ. Heidelberg, Theodor-Kutzer-Ufer, 6800 Mannheim 1, W. Germany
Geburtshilfe Frauenheilkd; 42(4):249-255 1982

In the last 10 yr we have studied 21 adenocarcinomas of the endocervix developing in women up to the age of 50. Sixteen of these women had taken oral contraceptives, in most instances continuously for 1 to 16 yr, on the av for 10 yr. During the same period of time we collected eight adenocarcinomas in situ of the endocervical mucosa, seven of which developed after 1 to 20 yr of use of oral contraceptives. Ten of the 16 patients with adenocarcinomas and 5 of those with adenocarcinomas in situ had taken oral contraceptives containing norgestrel as gestagen. The others had taken either norethisterone acetate or lynestrol. Histologically 8 of the 16 carcinomas were well-differentiated, 5 were mucoepidermoid and 3 microalveolar adenocarcinomas. In two of the five patients who had not taken oral contraceptives, the adenocarcinomas were well-differentiated, the remaining three were poorly differentiated but without mucoepidermoid qualities. In the women taking the oral contraceptives an adenomatous hyperplasia of the endocervix developed either prior to or at the same time as the adenocarcinoma. Eight of 10 rhesus monkeys (NCI) treated every 84-90 days for 10 yr with medroxyprogesterone acetate at doses 50x those prescribed for women developed the same types of adenocarcinomas. These studies strongly suggest that the use of gestagens for many yr is causally related to the development of these generally rare adenocarcinomas. These results warrant further investigations. (Author abstract) (29 Refs) (In GER)

66. TREATMENT WITH A LUTEINISING-HORMONE-RELEASING-HORMONE ANALOGUE (BUSERELIN) IN PREMENOPAUSAL PATIENTS WITH METASTATIC BREAST CANCER.

Klijn JG, DeJong FH
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Lancet; 1(8283):1213-1216 1982

Four premenopausal women with metastatic breast cancer were treated with a potent luteinizing-hormone-releasing-hormone (LHRH) analogue as a single first-line agent. Buserelin (6-D-ser-(bu1)-LHRH-(1-9)-ethylamide) was given in very high doses intravenously and then intranasally; ovarian function did not decrease within 1-2 wk, but after this period low to very low (postmenopausal) plasma estradiol levels were reached in all patients, accompanied by flushes. Two patients, however, subsequently showed transient peaks of plasma estradiol, probably due to a persistent follicle, which lasted for some wk without a rise in plasma luteinizing hormone, follicle-stimulating hormone, or progesterone. In two patients there was no significant change in the tumor, whereas in the other two patients there was remarkable improvement. (Author abstract) (22 Refs)

67. JUVENILE PAPILLOMATOSIS OF THE BREAST AND FAMILY HISTORY OF BREAST CARCINOMA.

Rosen PP, Lyngholm B, Kinne DW, Beattie EJ
Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 49(12):2591-2595 1982

Eighty-four patients included in the Juvenile Papillomatosis Registry were reviewed. The age of diagnosis ranged from 10-44 yr (mean, 21). Sixty-nine percent of patients were less than or equal to 20 yr of age. The left breast was affected slightly more often (52%) than the right (48%) when the lesion was unilateral. Two patients had bilateral lesions. Patterns of menarche, marital history, parity, and use of birth control pills were not exceptional for women in this age range. No instance was found of maternal use of estrogens during pregnancy. There were no instances of carcinoma developing after biopsy of juvenile papillomatosis, but a newly diagnosed patient had secretory carcinoma arising from juvenile papillomatosis. Two other examples of concurrent carcinoma were previously reported (ipsilateral lobular carcinoma in situ and contralateral secretory carcinoma). Particularly noteworthy is the finding that 26% of patients with information available reported that breast carcinoma had occurred in one or more female relatives. The majority were older, secondary relatives (grandmothers, great aunts), although maternal breast carcinoma (5 cases) was also reported. The mothers of both girls who had secretory carcinoma associated with juvenile papillomatosis had been treated for breast cancer. These findings, based on incomplete reporting, are cause for concern in two respects: the findings suggest that juvenile papillomatosis may be a marker for breast cancer for the patient's family, and they indicate a need for continued long-term follow-up of juvenile papillomatosis patients who may themselves be at increased risk. (Author abstract) (4 Refs)

68. ADJUVANT CHEMOTHERAPY FOR BREAST CANCER: AN OVERVIEW OF NSABP FINDINGS.

Fisher B, Redmond C, Elas G, Evans J, Foster R, Jochimsen P, Lawrence W, Lerner H, LiCalzi N, Margolese R, Poisson R, Sachs S, Shibata H, Sutherland C, Wallack M, NSABP Investigators
Dept. Surgery, Univ. Pittsburgh, Sch. Medicine, Pittsburgh, PA, 15261
Int Adv Surg Oncol; 5:65-90 1982

The salient findings which have been obtained from various National Surgical Adjuvant Breast and Bowel Project (NSABP) trials are overviewed and related to the results observed in clinical trials carried out by others. Information regarding new studies is provided. Effectiveness of a single agent (L-phenylalanine mustard; L-PAM), a combination of two drugs (L-PAM + 5-fluorouracil; PF), a three-drug combination (PF + methotrexate; PMF), and addition of tamoxifen (T) to chemotherapy is discussed. A significant advantage over L-PAM, both in disease-free survival as well as in survival, exists for all patients who received PF. When patients are considered overall, according to age, or according to age and nodal status, findings fail to demonstrate that PMF is superior to PF. Findings from 1,414 eligible patients with follow-up information and quantitative estrogen receptors (ER) indicate that when ER of tumors was less than 10 femtomole (fmol), no benefit resulted overall from the addition of T to PF. A difference in response was observed in two age groups; patients greater than or equal to 50 yr old whose tumors had ER greater than or equal to 10 fmol displayed a benefit, whereas those greater than or equal to 49 yr old demonstrated no improvement from the addition of T. Tolerance of any of the regimens was unrelated to patient age, despite the belief that older women are less tolerant of chemotherapy. Results indicate that NSABP data failed to substantiate the concept that regimens utilizing a greater number of agents are apt to be more beneficial. (15 Refs)

69. HEMATOPOIETIC DYSPLASIA AND MARROW HYPOCELLULARITY IN CHILDREN: A PRELEUKEMIC CONDITION.

Kobrinsky NL, Nesbit ME, Ramsay NK, Arthur DC, Krivit W, Brunning RD
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J Pediatr; 100(6):907-913 1982

Seven children with hematopoietic dysplasia were identified by morphologic criteria. The peripheral blood and bone marrow findings in these children were characterized by macro-ovalocytosis, progressive marrow hypoplasia, proteinaceous debris in the marrow interstices, and megaloblastoid changes. Six of the patients had major constitutional abnormalities including coarse or unusual facies (4), short stature (4), and mental retardation (4). These children were prone to recurrent bacterial infections prior to the onset of documented leukopenia. Chromosome studies of blood and bone marrow demonstrated a clonal abnormality involving the B, C, and E groups in 3/5 patients. An increase in the number of spontaneous chromosome breaks or radial figures was not observed. CFU-Cs were uniformly decreased in 5/5 patients, prior to the onset of leukopenia in one. Incomplete and transient responses to folic acid (3/4), androgens (1/4), and steroids (3/3) were noted. There were no responses to vitamin B12 in three patients or to ATG or other immunosuppressive therapies in four patients. One child has a sustained response to pyridoxine and one has had successful hematopoietic reconstitution by bone marrow transplantation. Three of the patients developed myelogenous leukemia 13, 47, and 100 mo, respectively after presentation. Two have died from leukemia and one from intracranial hemorrhage. Children with HD differ morphologically and clinically from adults with 'the preleukemic syndrome' by manifesting marrow hypocellularity and constitutional abnormalities. Both groups are at high risk for the development of progressive pancytopenia and myelogenous leukemia. Unlike those with Fanconi anemia, these children respond poorly to treatment with androgens and steroids. Results of bone marrow transplantation in one of the patients are encouraging. (Author abstract) (20 Refs)

70. ESTROGEN RECEPTOR PROTEIN IN ADENOMAS OF THE LARGE BOWEL.

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Dis Colon Rectum; 25(4):348-350 1982

Thirty adenomas of the large bowel, removed from 15 females and 15 males, were examined for the presence of estrogen receptor protein. The finding of positive binding capacity in 2 of the 30 adenomas supports the hypothesis that hormonal dependency does not play a major role in the development and growth of colorectal adenomas. (Author abstract) (15 Refs)

71. THE DESMOID TUMOR. II. ANALYSIS OF FACTORS POSSIBLY CONTRIBUTING TO THE ETIOLOGY AND GROWTH BEHAVIOR.

Hayry P, Reitamo JJ, Totterman S, Hopfner-Hallikainen D, Sivula A
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Am J Clin Pathol; 77(6):674-680 1982

Eighty histologically verified cases of the desmoid tumor (DT) have been analyzed with regard to factors possibly contributing to the etiology and/or growth behavior of this uncommon neoplasm. Considering the four statistical age components, the 'fertile' female and 'menopausal' varieties of the DT grew distinctly faster (0.1 less than p greater than 0.05 and less than 0.05), and the female 'juvenile' variety distinctly slower (0.1 less than p greater than 0.05) than the male DTs. In a visual estimate, the fertile female patients had a significant (p less than 0.01) predisposition to estrogen predominance, while fewer patients than expected displayed progesterone predominance or were at balance (p = NS and less than 0.01, respectively). Thirty-two percent of the patients with an abdominal DT had previously operated in the region of subsequent tumor growth. Significantly more pregnancies were observed in patients with abdominal DT than with extra-abdominal DT (p less than 0.05). On only one occasion did sigmoideoscopy reveal colonic polyposis (Gardner's syndrome). The most striking observation was, however, that up to 80% of the affected patients (compared with less than 5% in the normal control population, p less than 0.05) had multiple minor bone anomalies demonstrable by x-ray screening of the mandible, chest, and long bones. We suggest that a generalized (inherited or mutant) defect in growth regulation of connective tissue is the most important underlying cause for the DT. However, the other factors, including hormonal effects, trauma and pregnancy contribute to the growth behavior of the tumor. (Author abstract) (13 Refs)

72. THE DESMOID TUMOR. III. A BIOCHEMICAL AND GENETIC ANALYSIS.

Hayry P, Reitamo JJ, Vihko R, Janne O, Scheinin TM, Totterman S, Ahonen J, Norio R, Alanko A
Transplantation Lab., Univ. Helsinki, Haartmaninkatu 3, SF 00290 Helsinki 29, Finland
Am J Clin Pathol; 77(6):681-685 1982

We have carefully examined four patients with desmoid tumor (DT) and their 31 relatives. In three of four cases, biopsies of the DT demonstrated low yet significant amounts of estrogen but not progesterone receptors in the tumor cytosol. In the fourth case, where the receptors were not demonstrable, the affected patient was a menopausal woman and the receptors may have been blocked by endogenous estrogen. Fourteen of their 31 relatives demonstrated multiple minor bone malformations in x-ray screening of the skeleton. The inheritance of these malformations was compatible with an autosomal dominant trait with variable penetrance. These findings are compatible with our suggestion that the basic underlying cause for DT is an inherited defect in growth regulation of the connective tissue. When a trauma is superimposed on such an individual, a DT may result. The growth of the tumor is, however, controlled primarily by sex hormones, estrogen predominance over progesterone being inducive to tumor growth. (Author abstract) (17 Refs)

73. HORMONAL MANIPULATION OF PULMONARY METASTASES FROM CARCINOMA OF THE PROSTATE.

Morin ME, MacNealy GA, Tan A, Li YP, Engel G, Henneberry M
Dept. Radiology, Community Hosp. Springfield and Clark County, 2615 East High St., Springfield, OH, 45501
Urol Radiol; 4(1):23-27 1982

Chest roentgenograms and medical records for 91 consecutive patients having orchiectomy for advanced carcinoma of the prostate were reviewed. Six patients (57-85 yr old) thought to have prostatic pulmonary metastases were observed for several months after orchiectomy. Roentgenograms taken prior to orchiectomy were compared with those taken several months after surgery. Four of the six cases showed regression of pulmonary metastases over the 4 to 11-mo postoperative period; two cases did not respond. The two nonresponders both had been treated with diethylstilbestrol (DES) for 37 and 42 mo prior to development of lung metastases. An additional four patients (55-79 yr old) received DES rather than orchiectomy at a rate of 2 mg/day over a 3 to 9-mo period. These four patients also exhibited regression of pulmonary metastases. Antiandrogenic therapy alone apparently will result in regression of lung metastases and alleviation of the symptom complex of lymphangitic spread in the majority of patients who have not received prior hormonal manipulation. (19 Refs)

74. 3,4-BIS(3'-HYDROXYPHENYL)HEXANE - A NEW MAMMARY TUMOR-INHIBITING COMPOUND.

Kranzfelder G, Hartmann RW, Von Angerer E, Schonenberger H, Bogden AE
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J Cancer Res Clin Oncol; 103(2):165-180 1982

The syntheses of the hexestrol derivatives 3,4-bis-(3'-hydroxyphenyl)hexane (4a), 3,4-bis(4'-fluoro-3'-hydroxyphenyl)hexane (4b), 3,4-bis(3',4'-dihydroxyphenyl)hexane (4c) and 3,4-bis(3',4'-diacetoxyphenyl)hexane (4d) are described. All compounds showed a marked, competitive inhibition of the estradiol receptor interaction (Ka4c greater than Ka4a greater than Ka4d greater than Ka4b). Evaluated in the mouse uterine wt test compounds 4c and 4d almost reached the estrone effect, whereas 4a and 4b did not produce full uterotrophic response. Compounds 4a-d antagonized the estrone stimulated uterine growth of the immature mouse. Compound 4a (NSC-297170) exhibited a specific, dose-related growth inhibition of the estrogen responsive MCF-7 human breast tumor cell line. Tested on the 9,10-dimethyl-1,2-benzanthracene-induced hormone-dependent mammary adenocarcinoma of the Sprague-Dawley rat all compounds showed marked inhibition of tumor growth. As in all experiments compounds 4a and 4b, which is resistant to hydroxylation in 4' position exhibited an identical pattern of action, which is different from that shown by compound 4c, the effect of compound 4a cannot be explained by its possible catechol metabolite 4c. (Author abstract) (38 Refs)

75. INFLUENCE OF DAILY SUBCUTANEOUS ADMINISTRATION OF 6-METHYLPREDNISOLONE AND ORAL APPLICATION OF 30% SALINE SOLUTION ON TUMORIGENESIS INDUCED IN MOUSE STOMACH BY SINGLE APPLICATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner G, Habs M, Schmahl D
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J Cancer Res Clin Oncol; 103(2):207-209 1982

Low-dose dimethylbenz(a)anthracene (25 mg/kg po by gavage on day 1) produced papillomas in the forestomach of female C57BL/6 mice treated with 6-methylprednisolone (MP: 80 mg/kg/day sc on days 1-3) and 30% NaCl (0.25 ml/animal, days 1-3, 1 hr after MP, by gavage). Hyperplasia/hyperkeratosis was observed in 5/20 animals and papilloma in 12/20 animals. Median latent period for papilloma development was 25 days. The results indicate that in an altered environment small amounts of a chemical carcinogen suffice to induce tumors. (7 Refs)

76. THE EFFECT OF DIETARY RESTRICTION, ADRENALINE, HYDROCORTISONE AND SURGERY ON THE RATES OF DEATH OF 125IUDR-LABELLED, INTRAVENOUSLY INJECTED TUMOUR CELLS IN THE LUNGS OF MICE.

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Dept. Pathology, Univ. Queensland Medical Sch., Herston, Queensland 4006, Australia
Aust J Exp Biol Med Sci; 60(1):55-71 1982

Dietary restriction, adrenaline, hydrocortisone or surgery reduced the rate at which pulmonarily arrested 125IUdR-labeled murine tumor cells were lost within 7 hr of intravenous (iv) injection. Mice that had been adrenalectomized 10 days previously showed a normal intrapulmonary tumor cell loss rate with further surgery reducing this rate to approx half that observed in normal mice that had been subjected to surgery. Thus, although it is likely that adrenal hormones play an important role in decreasing the rate of early intrapulmonary tumor cell loss, additional factors must be implicated. Mice subject to dietary restriction, adrenaline, hydrocortisone or surgery had reduced levels of in vitro growth inhibitor(s) in their sera. Despite this, individual surgically treated animals showed no correlation between serum in vitro growth inhibitor levels and rate of loss of iv injected tumor cells from the lungs. Furthermore, the 24 hr pre-incubation of tumor cells in inhibitor-rich serum did not influence the subsequent loss rate of such cells following iv injection into mice. Electron microscopic studies indicated that dietary restriction, adrenaline and surgery reduced the rate of intravascular tumor cell death. The decreased tumor cell death rate in mice receiving these treatments could not be related, however, to any consistent morphological change in the pulmonary vasculature. The decreased rate of intravascular tumor cell death in treated mice was followed by an increased number of lung tumors with only one of the tumor lines studied, indicating that the intravascular death rate need not be a major determinant of pulmonary tumor incidence. (Author abstract) (23 Refs)

77. METASTATIC BREAST CARCINOMA: SEQUENTIAL HORMONOTHERAPY WITH TAMOXIFEN AND MEDROXYPROGESTERONE ACETATE. PRELIMINARY RESULTS.

Bosset JF, Pereal M, Hurteloup P, Altwegg T, Del Piano F, Colette C, Schraub S
Service de Radiotherapie, Centre Hospitalier Regional, 2, place Saint-Jacques, F-25030 Besancon Cedex, France
Bull Cancer (Paris); 69(2):170-171 1982

Thirty-two women (42-85 yr old; median age 63 yr) with metastatic breast cancer were treated with sequential tamoxifen (TX: 30 mg/day, on days 1-7) and medroxyprogesterone acetate (MP: 600 mg/day po, on days 8-15) in a Phase II trial. Each 15-day cycle of treatment was repeated without interruption for at least 6 wk prior to evaluation. Of the 32 patients, 27 were evaluable for response and 28 for toxicity. Among the 27 patients, 5 complete and 10 partial responses were observed; in 12 patients, tumor progression or no regression were noted. The median durations of complete and partial remissions were 6 mo (6-12 mo) and 7 mo (5-12 mo), respectively. Treatment was ended in two patients in partial remission at 7 and 11 mo, respectively, due to toxicity or tumor progression. The median delay prior to response was 4 mo (2-7 mo). Five cases of uterine hemorrhage were observed; in two such cases, treatment was halted after 1 and 7 mo, respectively. (8 Refs) (In FRE)

78. PROLIFERATIVE RESPONSES OF HUMAN PROSTATIC NEOPLASIA AND RAT PROSTATE IN ORGAN CULTURE (MEETING ABSTRACT)

Riches AC, Mistry D, Buchanan L, Dattani G, Weaver JP
Department of Anatomy and Experimental Pathology, University of St. Andrews, St. Andrews, Scotland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh Scotland. British Association for Cancer Research 78 pp., 1982.

In an attempt to provide a model for investigating hormone responsiveness and sensitivity to chemotherapy of prostatic neoplasia, the proliferative responses of human and rat prostate have been followed in organ culture using 125I-iododeoxuridine uptake (125IUdR) to monitor DNA synthesis. In serum free cultures, testosterone induced a marked increase in DNA synthesis in prostates from 4-6 month old rats, reaching maximal levels after 4 days in culture, after which the uptake decreases to control unstimulated levels. This proliferative response is dose dependent and is maximal at testosterone concentrations of 4 x 10-9M to 4 x 10-6M, whereas in prostates from 12 month old rats the response was less marked. Human benign prostatic hyperplasia showed a minimal response to testosterone stimulation, a similar pattern to that seen in the older rats. The proliferative response of human benign prostatic hyperplasia increases up to day 3 to 4 in culture and then declines in both control and hormone treated groups and may represent repair processes which appear to be hormone dependent. Explants from prostatic carcinoma were well maintained in organ culture but had to be carefully selected using frozen sections to obtain cellular areas in the transurethrally resected tissue samples. No marked changes in the histological appearance of the prostatic carcinoma explants were observed in the presence of testosterone, Estracyt or estradiol. Testosterone exhibited some stimulatory effects in 125IUdR uptake whereas both Estracyt (estramustine phosphate) and estradiol were weakly inhibitory. (no Refs)

IMMUNOLOGIC EFFECTS OF STEROID HORMONES

79. ABILITY OF TUMOR CELLS TO RESIST HUMORAL VS. CELL-MEDIATED IMMUNE ATTACK IS CONTROLLED BY DIFFERENT MEMBRANE PHYSICAL PROPERTIES.

Schlager SI
Dept. Microbiology, Univ. Notre Dame, Notre Dame, IN, 46556
Biochem Biophys Res Commun; 106(1):58-64 1982

Treatment of P815 murine mastocytoma cells with adriamycin increased their susceptibility to killing by antibody + complement (Ab-C) compared to controls; mitomycin C did not show this effect. Cells washed free of the drug and incubated in the drug-free medium regained control levels of susceptibility to Ab-C. Opposite effects of these two drugs on the susceptibility of P815 cells to killing by cytotoxic T-lymphocytes (CTL) were observed, ie, mitomycin C, but not adriamycin, increased the susceptibility to CTL killing. Cells washed free of drug and reincubated in drug-free medium reverted to control levels of susceptibility to CTL. P815 cells cultured with hydrocortisone were rendered more resistant, compared to controls, to Ab-C or CTL killing; epinephrine treatment had no effect on the susceptibility to either Ab-C or CTL attack. Cells washed free of hormone again reverted to control levels of susceptibility to Ab-C and CTL. Membranes from adriamycin-treated cells exhibited increased membrane fluidity compared to controls; mitomycin C had no effect. Hydrocortisone treatment decreases membrane fluidity while epinephrine had no effect. Mitomycin C decreased, and hydrocortisone increased, the net negative cell surface charge density. Adriamycin and epinephrine had no effect. Drug- or hormone-treated reverted cells were similar to control cells in membrane fluidity and surface charge. These results indicate that plasma membrane fluidity and cell surface charge are unique physical properties that control the susceptibility of tumor cells to Ab-C and CTL killing, respectively. (19 Refs)

80. EFFECT OF VARIOUS IMMUNOSUPPRESSIVE AGENTS ON THERAPEUTIC EFFICACY OF HISTOCOMPATIBLE MYELOTRANSPLANTATIONS.

Romanova AF, Timoshenko LI, Burka NI, Klimenko VI, Korotia TA
Res. Inst. Hematology and Blood Transfusion, Kiev, USSR
Vrach Delo; (3):25-29 1982

The effect of immunosuppressive agents on the therapeutic efficacy of bone marrow transplantation was studied in 42 women with hypoplastic anemia (HA) and in 25 women with depression of the hematopoiesis after radiotherapy and chemotherapy for Stage II-III ovarian and uterine cancer. Transplantation of the histocompatible bone marrow produced clinical improvement on 23/25 cancer patients and in 21/42 HA patients. Administration of antilymphocytic globulin in combination with corticosteroid hormones inhibited the cellular and humoral immunity and thus prevented the rejection of bone marrow graft. (no Refs) (In RUS)

81. IMMUNOGLOBULIN LOCALIZATION IN THE NORMAL HUMAN MAMMARY GLAND: VARIATION WITH THE MENSTRUAL CYCLE (MEETING ABSTRACT)

Budwit DA, Sasso R, Seigler HF, Georgiade NG, McCarty KS
Department of Pathology, Duke University Medical Center, Durham, NC
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Differences in immunoglobulin localization in benign versus malignant lesions of the breast and a prognostic value for IgG localization have been previously demonstrated. To determine whether menstrual cycling influences immunoglobulins in the breast as in the uterus, 53 women who underwent subcutaneous mastectomy (no hormones, debilitating disease, or medications which might influence pituitary-ovarian axis, no neoplasia, age 16 to 51) were studied. Immunoglobulin localization in tissue sections were determined using antibodies specific for IgG, IgA, IgM, and IgA secretory piece. The breast tissues were categorized into five histologicallly distinct menstrual cycle phases. Pericellur IgG localization was not seen in these 'normal' tissues. IgA localization was noted principally in the preovulatory phase of the cyce (phase II to III). IgM showed a similar trend. IgA secretory piece paralleled IgA localization. No correlation between IgA or IgM localization and plasma cell infiltration or between plasma cell infiltration and mestrual cycle phase could be documented. (2 Refs)

GENERAL REVIEWS ON STEROID HORMONES

82. NEW CONCEPTS ABOUT HORMONOTHERAPY OF BREAST CANCER.

Bonneterre J, Cappelaere P, Adenis L
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Gynecologie; 32(6):493-501 1981

Developments in hormone therapy (HT) for the treatment of breast cancer (BC) are reviewed. Greater knowledge of the mechanism of action at the cellular level of steroids and the development of technics for measuring hormone receptors in target tissue has encouraged the use of HT, particularly in BC. The mechanism of action of steroids, particularly estradiol, is discussed with regard to hormone-receptor complex formation and DNA synthesis. Hormones receptors may be measured using marked hormones. Other technics include autoradiography, immunofluorescence, and antireceptor antibodies. Seventy percent of breast tumors are estrogen receptor (ER)-positive. The occurrence of ER varies among primary and secondary tumors and local recurrences (85%, 78%, and 52%, respectively). Fifty-two per cent of breast tumors are progesterone receptor (PR)-positive. Variations also are observed for PR among primary and secondary tumors and local recurrences (57%, 38%, and 50%, respectively). The influence of menopausal status, age, lymphatic metastasis, pathology, endogenous hormones, site, and other parameters of hormone receptor status are discussed. The relationship between hormone receptor status and therapeutic response of breast tumors is considered. Antiestrogens (clomiphene, tamoxifen, and nafoxidine), aminoglutethimide, and aromatase inhibitors may be used in HT of breast cancer. HT of polymetastatic breast cancer and adjuvant HT are described. (35 Refs) (In FRE)

83. MALIGNANCY - TUMOUR MARKERS IN CLINICAL PRACTICE.

Buckman R
Ludwig Inst. for Cancer Res., Sutton, England
J Appl Med; 8(5):355-360 1982

The current status of both tumor-derived and tumor-associated markers are reviewed. Clinically useful markers include human chorionic gonadotropin, alpha fetoprotein, carcinoembryonic antigen, eutopic hormones, estrogen receptors, paraproteins, prostatic acid phosphatase, epithelial membrane antigens and T- and B-cell markers. Applicability of the markers to various neoplasms with regard to diagnosis, prognosis, metastases and screening studies is tabulated. (57 Refs)

84. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Hormones as etiological agents in neoplasia are discussed. The basic properties of human hormones are reviewed, and general considerations in the detection of hormonal activity are listed. Brief general comments are presented on tumors in peripheral areas illustrating the diversity of pathogenic mechanisms by which hormones can produce tumors. Peripheral tumors are of two kinds: those affecting non-hormone-secreting organs, which do not feed back (as with the mammary gland), and those affecting peripheral hormone-secreting organs, which do. The best example of the former is the mammary tumor, and good examples of the second type are thyroid and ovarian tumors. Other tumors which are hormonally related include adrenal tumors which are unique in that they can give rise to four or more types of tumors - estrogen, androgen, glucocorticoid, and mineralocorticoid secreting - and in that they have different types of inductive mechanisms. Renal cortical carcinomas are induced by estrogens in male hamsters. Human placental lactogen stimulates carcinogenesis in young rats. It promotes mammary tumorigenesis during pregnancy, both directly and indirectly, through its promotion of progesterone secretion by the ovary. Thyrocalcitonin is the hypocalcemic polypeptide hormone secreted by the medullary cells of the thyroid. These cells can give rise to medullary thyroid carcinoma. (286 Refs)

85. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982

Recent studies on relationships between hormone status and breast cancer in women are reviewed. The pathophysiological aspects of estrogens, prolactin, dehydroepiandrosterone and dehydroepiandrosterone sulfate and therapeutic significance of estrogen and prolactin receptors are discussed. (57 Refs) (In ITA)

86. HISTOLOGICAL AND CYTOLOGICAL PROGNOSIS OF BREAST CANCER.

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Rev Med Brux; 3(3):133-137 1982

Various histological and cytological classifications of breast cancer (BC) are discussed in relation to prognosis. The diagnostic value of the mean nuclear diameter in the determination of the prognosis for BC is described. A technic for relating mean nuclear size to histoprognostic factors in BC are described. The technic is reproducible and shows a good correlation with earlier classification schemas. The prognostic significance of estrogen receptors (ER) and menopausal status in BC is discussed. Sixty percent of patients with BC are ER-positive. After menopause, the number of ER-positive cases increase. The relationship between ER status and response to hormone therapy is discussed. Some studies of ER status seem to indicate that the presence of ER status neither influences the duration of tumor-free survival, the frequency of lymphatic involvement, nor the hope of favorable response to chemotherapy. ER receptors characterize tumors with slowly dividing cells. BC tumors in premenopausal women show high rates of cell division, less cell differentiation, and lower concentrations of ER. (36 Refs) (In FRE)

87. ADJUVANT ENDOCRINE THERAPY AND CHEMOTHERAPY FOR BREAST CANCER.

Heuson JC, Paridaens R

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Rev Med Brux; 3(4):209-216 1982

Results of adjuvant therapy for breast cancer are reviewed. The concept of surgical oophorectomy was proposed as adjuvant therapy almost 100 yr ago, but two clinical trials that were published revealed that there were almost no benefits from the procedure. Castration by ovarian radiation provided benefits that were marginal at best. Early single agent chemotherapy (cyclophosphamide) provided 10% overall survival and also survival without recurrence. Best results were obtained in the 1970s with the introduction of combination adjuvant chemotherapy. Significant increases in disease-free interval were obtained, and there was a 57% reduction in failure rate and a 54% reduction in mortality. Several combination protocols worked equally well, and whether the treatment lasted 6 or 12 mo was not a critical factor. The dose that the patient received was the critical factor. Only full doses were effective in improving the survival rate in advanced breast cancer. Combination chemotherapy seemed equally effective in pre- and postmenopausal women. The effectivenes of combination chemotherapy was increased with the administration of the antiestrogen tamoxifen for estrogen-rich tumors. (23 Refs) (In FRE)

OTHER RELATED STUDIES

88. THE FOOD-ENTRAINED PROLACTIN AND CORTISOL RELEASE IN LATE PREGNANCY AND PROLACTINOMA PATIENTS.

Quigley ME, Ishizuka B, Ropert JF, Yen SS

Dept. Reproductive Medicine (T-002), Univ. California, San Diego, Sch. Medicine, La Jolla, CA, 92093

J Clin Endocrinol Metab; 54(6):1109-1112 1982

Abrupt and concomitant increments in circulating cortisol and PRL levels in association with food intake at noon were observed in hyperprolactinemic pregnant women. During late pregnancy, the quantitative release was at least 12-fold greater for PRL and substantially more for cortisol compared to values in nonpregnant women. In contrast, patients with hyperprolactinemia due to prolactinoma exhibited an absence of the PRL response to the noon meal and a significantly smaller rise in cortisol, suggesting an independent mechanism for the release of these two hormones due to food ingestion. These observations may be important for future elucidation of neuroendocrine links between feeding and metabolic homeostasis in pregnancy. (Author abstract) (35 Refs)

89. EFFECT OF HYPOTHALAMIC AND PITUITARY IRRADIATION ON PUBERTAL DEVELOPMENT IN CHILDREN WITH CRANIAL TUMORS.

Rappaport R, Brauner R, Czernichow P, Thibaud E, Renier D, Zucker JM, Lemerle J

Hopital des Enfants Malades, 149, rue de Sevres, 75730 Paris Cedex 15, France

J Clin Endocrinol Metab; 54(6):1164-1168 1982

The purpose of the present study was to report on gonadotropin function and puberty of a large group of children treated by cranial irradiation for cranial and neck tumors and medulloblastoma. Forty-five children of pubertal age were investigated. The mean interval time since radiation was 5 2/12 yr. Gonadotropin and gonadal function were evaluated by clinical criteria, plasma sex steroids, and plasma LH and FSH responses to LRH. Puberty was complete or progressing normally in 31 cases and was abnormal in 14 cases. Severe gonadotropin deficiency, with lack of or slow progression of puberty and decreased LH and FSH responsiveness to LRH, was observed in five cases; two of these had moderately elevated plasma PRL levels. Secondary amenorrhea or lack of pubertal progression was found in five other cases. GH deficiency was associated with gonadotropin deficiency in 9 of these 10 cases. Adrenal function, estimated by basal dehydroisoepiandrosterone, dehydroisoepiandrosterone sulfate, and estrone, was normal according to pubic hair stages. In conclusion, complete or partial gonadotropin deficiency can be the consequence of cranial irradiation in children receiving 6,000 rads or less. It is usually associated with GH deficiency. The site of the damage on the pituitary gland or the hypothalamus remains to be demonstrated. (Author abstract) (22 Refs)

90. PITUITARY ADENOMAS: AN IMMUNOCYTOCHEMICAL STUDY OF 147 TUMORS IN 140 PATIENTS (MEETING ABSTRACT)

Mukai K
Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN
Lab Invest; 46(1):59A 1982

Immunocytochemical study of prolactin (Prl), growth hormone (GH), ACTH, gonadotropins (LH/FSH (luteinizing hormone/follicle stimulating hormone)), and TSH (thyroid stimulating hormone) was performed in 147 pituitary adenomas from 140 patients (male:female 3:4; 13 to 81 years old), and the results were correlated with the clinical manifestations. Eighty-six tumors were positive for one hormone, eight tumors for two hormones, and 53 tumors were negative for all hormones tested. In the first group, there were 40 Prl-positive tumors in females (amenorrhea-galactorrhea, 30; amenorrhea, seven; hirsutism, one; delayed puberty, one; and hypopituitarism, one); 19 Prl-positive tumors in males (hypogonadism, five; galactorrhea, two; gynecomastia, two; delayed puberty, one; growth retardation, one; and no specific endocrine symptoms, eight); 12 GH-positive tumors (acromegaly, 11; and amenorrhea-galactorrhea, one); nine ACTH-positive tumors (Cushing's syndrome, seven; Nelson's syndrome, one; and hirsutism, one); and six LH/FSH-positive tumors (no specific endocrine symptoms, six). The second group consisted of six Prl- and GH-positive tumors (acromegaly, six); one Prl- and ACTH-positive tumor (amenorrhea-galactorrhea, one) and one Prl- and TSH-positive tumor (no specific endocrine symptoms, one). The third group was comprised of 53 tumors without hormone production by immunocytochemistry (amenorrhea-galactorrhea, three; amenorrhea, two; growth retardation, one; and no specific endocrine symptoms, 47). (no Refs)

91. EVIDENCE FOR THE ROLE OF ANDROGENS IN THE FEEDBACK CONTROL OF GONADOTROPHIN SECRETION IN THE HUMAN FEMALE.

Gray P, Potgieter GM, Slabber CF, Veldsman JJ
Dept. Chemical Pathology, Univ. Orange Free State, Bloemfontein, South Africa
S Afr Med J; 61(22):837-838 1982

The effect of androgens on the luteinizing hormone (LH) response to LH-releasing hormone (LH-RH) is fairly well documented. However, the evidence concerning the effect on follicle-stimulating hormone (FSH) is less convincing and clear-cut. We administered LH-RH to a patient with an androgen-producing adrenal tumor both before and after removal of the tumor. Before operation, testosterone levels were elevated and estradiol levels reduced. There was no response of either LH or FSH levels to LH-RH on two separate occasions. Postoperatively LH-FSH values rose sharply, to 404% and 170% above basal levels respectively. The data suggest that androgens do play a role in the feedback control of both LH and FSH secretion. (Author abstract) (11 Refs)

92. THE RATIONAL APPLICATION OF ENDOCRINOLOGICAL AND RADIOLOGICAL METHODS IN THE DIFFERENTIAL DIAGNOSIS OF HIRSUTISM IN WOMEN.

Moltz L
Abteilung fur Gynakologische Endokrinologie Sterilitat und Familienplanung, Frauenklinik, Klinikum Steglitz Freie Universitat Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Geburtshilfe Frauenheilkd; 42(4):321-326 1982

The intensity and duration of the clinical symptoms and signs determine the type and spectrum of the necessary and essential diagnostic measures in women with signs of hirsutism. Women with specific disease entities and women who desire pregnancy are in a different category. When severe signs of androgenization (virilism) and obvious progression are noted the hormones testosterone and dehydroepiandrosterone (T and DS) must be determined in the peripheral blood. When the peripheral testosterone value exceeds 1.5 ng/ml and when the peripheral dihydroepiandrosterone value exceeds 7,000 ng/ml the existence of a virilizing tumor must be excluded as soon as possible. The exclusion or localization of a small androgen producing tumor can be achieved with the greatest certainty with selective catheterization. In patients with mild androgenization a specific diagnostic work-up is not necessary. (Author abstract) (25 Refs) (In GER)

93. MENOPAUSAL ENDOCRINOLOGY AND MANAGEMENT.

Korenman SG
Dept. Medicine, Univ. California Los Angeles-San Fernando Valley Program, Veterans Admin. Hosp., Sepulveda, CA, 91343
Arch Intern Med; 142(6):1131-1136 1982

Entry into menopause is associated with a severe diminution of ovarian estrogen and progesterone secretion and a reduction of circulating androgens, although, in the presence of ovaries, a degree of testosterone secretion persists. Menopause is associated to a varying degree and severity, with hot flashes a disorder of central thermoregulation - progressive sex tissue atrophy, and accelerated bone mineral loss that eventually leads to a substantial prevalence of osteoporosis, with spine, hip, and radial fractures, particularly in thin, inactive smokers with low calcium intake. Treatment with estrogens eliminates hot flashes and sex tissue atrophy and prevents osteoporosis. Unfortunately, oral estrogen therapy results in overstimulation of the liver, producing secreted proteins and an increased risk of endometrial carcinoma and gallbladder disease. The addition of a progestogen will diminish the risk of endometrial carcinoma, presumably by reducing estrogen-receptor concentration and increasing estradiol dehydrogenase activity but will usually result in vaginal bleeding in women with uteri. The use of estrogen therapy with or without a progestin should be an informed joint decision of physician and patient that must be reevaluated regularly as new information becomes available. (Author abstract) (39 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. CHANGES OF THE DIURNAL RHYTHM OF PLASMA 11-HYDROXYCORTICOSTEROIDS IN RELATION TO MALIGNANT NEOPLASMS AND PRECANCEROSES IN OTOLARYNGOLOGY.

Cisarik A, Valdman V
Otolaryngologicke oddelenie, OUNZ-NsP, Holeho 20, 080 01 Presov, Czechoslovakia
Cesk Otolaryngol; 31(2):98-101 1982

The circadian rhythm of plasma 11-hydroxycorticosteroids (HCS) was studied in 269 patients with benign and malignant diseases of the ear-nose-throat region. Polyps of the nasal cavity were diagnosed in 102 patients, laryngeal papillomatosis in 8, chronic hypertrophic laryngitis in 31, benign tumors in 44, precanceroses in 17 , and malignant tumors in 67. Inverted circadian rhythm of HCS excretion (the levels measured in the afternoon were equal to or higher than those measured in the morning) in 70% of the patients with malignant tumors, in 30% of those with precanceroses, in 11.5% of those with benign tumors, in 26% of those with chronic hypertrophic lar-

HE 20.3173/2

yngitis, in 37.5% of those with laryngeal papillomatosis and in 40.8% of those with polyps of the nasal cavity. The findings indicates the predominance of normal circadian rhythm of HCS excretion in the patients with benign tumors and nonneoplastic diseases of the ear-nose-throat region. Four-stage collection of blood samples is recommended for monitoring the plasma HCS levels. (8 Refs) (In SLO)

2. REVIEW OF STUDIES ON ESTROGEN BIOSYNTHESIS IN THE HUMAN.

Siiteri PK
Dept. Obstetrics, Gynecology, Reproductive Sciences, Reproductive Endocrinology Center, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(8,Suppl):3269s-3273s 1982

While the gonads and placenta are usually thought of as the principal sites of estrogen synthesis, many other tissues are now known to contain the aromatase enzyme. Despite a wealth of information, the functional significance, if any, of this widespread distribution is not yet clear. Nonetheless, elevated estrogen production resulting from either an apparent increase in enzyme activity or increased substrate availability in blood can have important effects on target tissues such as the breast, uterus, and bone. Our early studies suggesting that aromatase inhibitors can effectively reduce the impact of peripheral estrogen synthesis have been amply confirmed by the elegant studies of Santen and others. Many previous studies have suggested that aromatase activity may be present in breast tumors. The profound implications for growth of estrogen-sensitive tumors led us to reevaluate this question. Using a sensitive modification of our original radiometric aromatase assay, we have found detectable activity in only about 40% of human breast tumors (n = 100). Only rarely (1/100) does the aromatase activity exceed 1.0 pm/hr/g tissue or 0.001% of that found in the human placenta. These quantitative results contradict several published reports which suggest that most breast tumors contain biologically significant levels of aromatase activity. (Author abstract) (54 Refs)

3. AROMATASE IN THE CENTRAL NERVOUS SYSTEM.

Naftolin F, MacLusky NJ
Dept. Obstetrics and Gynecology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(8,Suppl):3274s-3276s 1982

Central (central nervous system and pituitary) aromatization appears to be a fundamental process for endocrine control and development. Metabolism of androgens to estrogens and the subsequent metabolism of estrogens have been proven in many species, including humans, and linked to estrogen action. Thus, aromatization appears to initiate or to be involved in activities of importance to endocrine function at the central level and their effects peripherally. In the context of breast cancer, central aromatization relates to the control of gonadotrophins and other pituitary-brain hormones which may effect metabolism at the level of the breast. For example, follicle-stimulating hormone can increase aromatization and may be a factor in the control of such metabolism in breast tissue. (Author abstract) (27 Refs)

4. OBESITY, ANDROGENS, ESTROGENS, AND CANCER RISK.

Kirschner MA, Schneider G, Ertel NH, Worton E
Newark Beth Israel Medical Center, 201 Lyons Ave., Newark, NJ, 07112
Cancer Res; 42(8,Suppl):3281s-3285s 1982

Obesity is associated with increased incidence of cancers arising from tissues responsive to estrogenic stimulation, including endometrium, breast, and prostate. We thus wished to explore estrogen production and its origin in obesity in an attempt to provide a possible hormonal link to explain increased cancer risk. Studies of the hormonal milieu of obese men and women revealed several abnormalities of sex hormone production and metabolism. (a) Androstenedione production rates are elevated and serve as prehormones of both testosterone and estrogens. (b) Extragonadal aromatization of androgens to form estrogens (androstenedione to estrone and testosterone to estradiol) is elevated, resulting in (c) increased production rates of estrogens. The obese person is thus chronically exposed to hyper-estrogenemia. In addition, obesity is associated with other alterations of sex hormone metabolism such as decreased levels of sex hormone-binding globulin and increased metabolic clearance rates of several hormones. After weight loss to ideal body weight, there appears to be normalization of androgen and estrogen production rates, as well as circulating hormone levels; however, metabolic abnormalities such as increased aromatization of androgens to estrogens and accelerated metabolic clearance rates of androstenedione remain abnormal. (Author abstract) (65 Refs)

5. RELATIONSHIP OF OBESITY TO BLOOD ESTROGENS.

Zumoff B
Div. Endocrinology and Metabolism, Dept. Medicine, Beth Israel Medical Center, New York, NY, 10003
Cancer Res; 42(8,Suppl):3289s-3294s 1982

It has become conventional wisdom that estrogenic stimulation of breast tissue has something to do with the causation of breast cancer and that the reason obesity is a risk factor for breast cancer is that obese women are hyperestrogenized. However, it has been very difficult to demonstrate that excessive exogenous estrogen increases the incidence of breast cancer, that endogenous estrogen excess is present in breast cancer, or that obese women are hyperestrogenized. We have examined the last question by measuring 24-hr mean plasma estrone and estradiol levels in the midfollicular phase in 18 healthy, regularly cycling, very obese (53 to 218% above ideal weight) women and 16 regularly cycling, age matched, nonobese control women. Unlike obese men, the obese women showed no significant elevation of either estrone or estradiol. Their av estrone level was 72 compared with 64 pg/ml in controls; their average estradiol level was 65 compared with 57 pg/ml in controls. In the combined group (obese plus nonobese), there was a significant correlation of percentage of deviation from ideal weight with plasma estrone ($y = 63 + 0.12x$; p less than 0.05) but not with estradiol. This correlation supports the current hypothesis that there is increased androstenedione/estrone conversion (ie, increased aromatase activity) in obesity. The reason plasma estrone levels are not significantly elevated in obese women is that the small amount derived from androstenedione is swamped by the much larger amount derived from ovarian secretion, which is apparently unaffected by obesity. Unless there is increased local formation of estrogens in the breast tissue of obese women, the absence of elevated plasma estrogens in them means that their breasts are not 'seeing' increased estrogen levels. Thus, endogenous hyperestrogenization is unlikely to be a causative factor of breast cancer in obese women. (Author abstract) (48 Refs)

6. IN VITRO ASSAYS OF AROMATASE AND THEIR ROLE IN STUDIES OF ESTROGEN FORMATION IN TARGET TISSUES.

Weiss J
Div. Reproductive Biology, Dept. Obsterics/Gynecology, Milton S. Hersey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(8,Suppl):3295s-3298s 1982

In recent yr, there has been increasing recognition of the importance of steroid aromatization in organs besides the steroidogenic ones. Estrogens formed from C-19 precursors in peripheral tissues can clearly contribute to the levels of estrogens in the circulation, while aromatization in target cells may be an important determinant of the concentration of estrogens to which a particular population of target cells is exposed. Assays sufficiently sensitive and simple enough to permit quantification and characterization of aromatase activity in peripheral and target tissues are now available. One of these, based on the quantification of 3H2O formed from [1-beta-3H]androstenedione has, in our hands, a sensitivity of 15 fmol, is highly reproducible, and is relatively simple. It has been validated for stoichiometry between amounts of 3H2O and [6,7-3H]estradiol formed from [1-3H]androstenedione and [6,7-3H]androstenedione, respectively. Using this assay, we have been able to quantify aromatase activity in discrete brain nuclear regions dissected from Vibratome sections of fetal rat brains and thereby to identify in discrete areas sex differences and temporal changes during development that are obscured when larger tissue specimens are used. However, aromatase activity in brain nuclei as well as other target organs, including breast tissue, is likely to be concentrated in specialized cell populations. This heterogeneity limits the interpretation that can be placed on data obtained from standard 'test tube' assays on homogenized tissue. We have used quantitative cytochemical assays for enzymes and cytochrome P-450 to identify regional specialization in the membrana granulosa of preovulatory follicles and localize cells that may be involved in steroidogenesis, including aromatization. Our findings underscore the need for new quantitative cytochemical and immunocytochemical assays to localize and to measure the amount and activity of aromatase in situ within identified populations of target cells. (Author abstract) (29 Refs)

7. MULTIPLE FORMS OF AROMATASE AND RESPONSE OF BREAST CANCER AROMATASE TO ANTIPLACENTAL AROMATASE II ANTIBODIES.

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Cancer Res; 42(8,Suppl):3299s-3306s 1982

Two distinct aromatase-active protein complexes are solubilized by use of deoxycholate and separated by diethylaminoethyl-cellulose chromatography from lyophilized powder of 900 x g precipitate fraction of human term placenta. Aromatase activity to produce estriol, the major estrogen of human pregnancy, was designated to be aromatase I activity and measured by estriol formation from 1-6alpha-hydroxytestosterone. Aromatase II activity was the designation for that which produces estrone plus estradiol and was measured by androstenedione aromatization. Aromatases II and I are eluted with 0.25 M and 0.5 M Tris buffer, respectively, from diethylaminoethyl-cellulose column in an Mr 2 million soluble complex. Each has a minimum active Mr 135,000 subunit, which is isolated by Bio-Gel filtration in the presence of detergents, and consists of a reduced nicotinamide adenine dinucleotide phosphate:cytochrome P-450 reductase (Mr 83,000) and a cytochrome P-450 (Mr 52,000). Aromatase II was found to be the major aromatase, containing approximately 5x more aromatase activity, reduced nicotinamide adenine dinucleotide phosphate:cytochrome c reductase activity, cytochrome P-450, and protein than did aromatase I. Antibodies raised in rabbits against aromatase II and its reductase suppressed aromatase II activity of breast cancer tissues, as well as of adult male lung tissue, placental microsomes, and solubilized aromatase. The breast carcinoma specimens responded to the antibodies in different degrees, but there was no response to antibodies against rat liver cytochrome P-450. The results indicate similar antigenic structures for breast cancer and placental aromatase but not for rat liver cytochrome P-450. (Author abstract) (29 Refs)

8. OVERVIEW OF RECENT DEVELOPMENT OF AROMATASE INHIBITORS.

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Cancer Res; 42(8,Suppl):3312s-3314s 1982

Since the first publication in 1973 concerning aromatase inhibitors, several effective compounds have been reported by a number of investigators. Our studies with 4-hydroxyandrostene-3,17-dione, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatrienedione indicate that these compounds cause rapid competitive inhibition of the enzyme. Aminoglutethimide binds competitively to cytochrome P-450 and inhibits a number of steroid hydroxylations but is more active as an aromatase inhibitor. 16alpha-Bromoandrogens and 7alpha-(4'-amino)phenylthioandrostenedione are also reported to be aromatase inhibitors. As yet, only some of these compounds have been evaluated in vivo, but all appear to be similarly effective in inhibiting aromatization in breast tumors in vitro. Recent interest has focused on enzyme inactivators or 'suicide' inhibitors. Such compounds act as substrates for the enzyme but are converted by the normal catalytic mechanism of the enzyme to reactive intermediates. These then bind covalently to the active site of the enzyme causing loss of activity. Active site-directed inhibitors are usually quite specific and have long-lasting effects in vivo. A number of new compounds, as well as some of the above compounds, appear to be inactivators of aromatase and are potentially interesting as agents for hormone-dependent breast cancer therapy. (Author abstract) (42 Refs)

9. BASIC STUDIES ON AMINOGLUTETHIMIDE.

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Cancer Res; 42(8,Suppl):3315s-3321s 1982

Aminoglutethimide (AG), a bicyclic substance with two optically active isomers, inhibits the cholesterol side-chain cleavage (SCC) and aromatase systems by blocking the terminal cytochrome P-450s. AG interacts with these cytochromes to induce typical Type II, low-spin spectra; the amount of spectral change correlates directly with the amount of enzymatic inhibition. AG acts by preventing reduction of the cytochrome, an obligate step preceding oxygenation of substrate. The apparent Ki of D(+)-AG is about 2.5x less than the Ki of L(-)-AG in inhibiting SCC and about 40x less in inhibiting aromatase. The spectral Ks ratios of the D- and L- enantiomers for

P-450SCC and P-450aromatase are 2.5 and 5, respectively, in the presence of substrate. The slope of the substrate concentration vs inhibition curves is less than 0.1 and extends over 2 logarithmic units of substrate concentration. By in vivo rabbit and rat assays for SCC, D-AG is 5 and 25x more potent than L-AG. In women, AG rapidly lowers estrogen and progesterone levels in the luteal phase of the menstrual cycle and in early pregnancy, eliciting a reflex release of luteinizing hormone in the luteal phase. In postmenopausal, adrenalectomized, ovariectomized women, AG prevents the aromatization of administered androstenedione. In inhibition studies in women, plasma steroid concentrations were inversely proportional to AG levels, which were about 20 to 30 uM. This level of AG, which approximates the apparent KiS of the SCC and aromatase systems, causes a decrease in hormone levels of about 50%. (Author abstract) (11 Refs)

10. A NEW HYPOTHESIS BASED ON SUICIDE SUBSTRATE INHIBITOR STUDIES FOR THE MECHANISM OF ACTION OF AROMATASE.

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Cancer Res; 42(8,Suppl):3327s-3333s 1982

Recently, it was discovered that 4-hydroxy-4-androstene-3,17-dione, 4-androstene-3,17-trione, and 1,4,6-androstatriene-3,17-dione, compounds previously reported to be competitive inhibitors of aromatase, cause a time-dependent loss of aromatase activity in human placental microsomes. We report here that 1,4-androstadiene-3,17-dione (Ki 0.32 uM; Kinact 0.91 x 10(-3)/sec) and testolactone (Ki 35 uM; Kinact 0.36 x 10(-3)/sec) also cause a similar loss of aromatase activity. The mechanism which explains the unexpected loss of activity caused by these five inhibitors is neither established nor apparent from current theories of the enzyme mechanism of action of aromatase. We propose an inactivation mechanism based on a new hypothesis for estrogen biosynthesis in which the third enzyme oxidation carried out by aromatase results in the formation of an enzyme-bound intermediate. This intermediate is released as an aromatized product via a facile elimination reaction which simultaneously regenerates the unaltered active enzyme. Various structural modifications made in these five inhibitors are hypothesized to redirect this elimination reaction so that the steroid intermediate remains covalently attached to the enzyme instead of being released as an aromatized product. (Author abstract) (24 Refs)

11. SUBSTITUTED C19 STEROID ANALOGS AS INHIBITORS OF AROMATASE.

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Cancer Res; 42(8,Suppl):3334s-3337s 1982

Various C19-steroidal derivatives have been synthesized and evaluated in biochemical assays for their ability to inhibit the biosynthesis of estrogens. Steroids with substitutions on the A or B ring were prepared by Michael addition of various thiol reagents to appropriate dienone intermediates. An in vitro assay using human placental microsomes was used to evaluate aromatase-inhibitory properties. Synthesized compounds that exhibited high inhibitory activity were further evaluated under initial velocity conditions to determine apparent Ki values. Several 7alpha-substituted androstenediones were effective competitive inhibitors and have apparent Ki values ranging from 18 to 69 nM, with the apparent Km for androstenedione being 63 nM. The most effective competitive inhibitor tested is 7alpha-(4'-amino)phenylthioandrost-4-ene-3,17-dione with an apparent Ki of 18 nM. Derivatives of this 7alpha-thioether compound that contain alkylating moieties have been prepared as potential irreversible enzyme inhibitors and demonstrate varying abilities to inactivate the aromatase enzyme. The results of these studies demonstrate that large chemical functionalities such as an aromatic ring with polar substituents can be accommodated in or near the active site of aromatase and, in some cases, can enhance the affinity of the enzyme for the inhibitors. (Author abstract) (16 Refs)

12. ESTROGEN SYNTHESIS IN HUMAN BREAST TUMOR AND ITS INHIBITION BY TESTOLOLACTONE AND BROMOANDROSTENEDIONE.

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Cancer Res; 42(8,Suppl):3338s-3341s 1982

A total of 53 tumors have been examined for estrogen synthesis from androstenedione and assayed for estradiol receptors. It was found that of the 40 tumors that metabolized androstenedione to estrogens, 17 tumors were estradiol receptor negative and 23 tumors were estradiol receptor positive. Of the 13 tumors that did not synthesize estrogens, 7 tumors were receptor negative and 6 tumors were receptor positive. No correlation was found between the ability of the tumor to synthesize estrogens and the presence or absence of estradiol receptors. The inhibition of aromatase enzyme in human breast tumors by delta(1)-testololactone, testololactone, and 6alpha-bromoandrostenedione and 6beta-bromoandrostenedione was investigated. Estrone and estradiol synthesis from androstenedione was reduced in five tumor incubations by the presence of 0.2 mM delta(1)-testololactone and testololactone. 6alpha- and 6beta-bromoandrostenedione (2.0 uM) were also shown to block estrogen synthesis in five tumors. Furthermore, Lineweaver-Burk plots revealed that all four compounds were competitive inhibitors of androstenedione aromatization. An apparent Km of the aromatase enzyme for androstenedione of 0.08 uM and a Vmax of 23 pmol of estrone synthesized per g tumor per hr were determined for one human breast tumor specimen. The use of an aromatase inhibitor such as delta(1)-testololactone in the treatment of breast cancer should be reconsidered. Data from one patient with advanced cancer of the breast, responding to previous oophorectomy and adrenalectomy and treated with large doses of delta(1)-testololactone, are presented to illustrate the significance of successful treatment by scientific approaches. (Author abstract) (25 Refs)

13. BIOCHEMISTRY OF AROMATASE: SIGNIFICANCE TO FEMALE REPRODUCTIVE PHYSIOLOGY.

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Cancer Res; 42(8,Suppl):3342s-3344s 1982

The formation of estrogens in mammals via aromatase involves the relatively unique capacity to form an aromatic ring de novo in contrast to most other aromatic substances (essential amino acids) which are obtained only in the diet. The reaction is the only example of a cytochrome P-450 system which resides in both the mitochondrial and microsomal fractions of the cell. It occurs widely throughout the body in diverse tissues and functions via both de novo synthesis and transformation of prehormones (androstenedione and testosterone). It is found widely in animal species in both the brain and gonads even in phylogenetically primitive species. Placental aromatase appears to be associated with the evolution of viviparity and an extended gestational period in utero. Follicular aromatase which is dependent upon follicle-stimulating hormone stimulation appears to be essential for oogenesis, ovulation, and normal luteal functions while central nervous system aromatase serves to determine sexual behavior and the neurohormonal link to the hypothalamus and pituitary for ovarian cyclicity. While estrogens are the key to pituitary, breast, and endometrial growth and development, this hormone is one of the few examples of an endogenous steroid that has been implicated as a carcinogen or a stimulant for carcinogenesis. (Author abstract) (18 Refs)

14. IN VIVO EFFECTS OF DELTA1-TESTOLOLACTONE ON PERIPHERAL AROMATIZATION.

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Cancer Res; 42(8,Suppl):3345s-3348s 1982

To evaluate the in vivo effect of delta(1)-testololactone on peripheral aromatization, studies were performed on seven postmenopausal women with metastatic breast cancer. Androstenedione levels were increased with all doses of testololactone tested, while estradiol rose with only the 250-and 500-mg dosages. With administration, there was a significant decrease of estrone. The addition of adrenal suppression (dexamethasone) significantly lowered androstenedione but had no effect on estrone or estradiol levels. Long-term therapy with the 250-mg dosage showed continual suppression of estrone with no escape being observed. Studies to determine the reason for the increase of estradiol with testololactone suggested cross-reactivity of the antibody with in vivo metabolites of the drug. However, these possible metabolites did not bind to uterine cytosol estrogen receptors. The decrease in estrone with testololactone administration presumably explains its antitumor properties. In postmenopausal women, the primary source of circulating estrone is the peripheral aromatization of an adrenal androgen, androstenedione, while the major source of estradiol is the peripheral conversion of estrone. Direct glandular secretion of either estrogen by the adrenal glands or ovaries is minimal. Compounds which inhibit peripheral aromatization should lower endogenous estrogen levels and would be of clinical interest in the treatment of conditions such as metastatic breast cancer. DELTA(1)-Testololactone has been shown to inhibit placental aromatization in vitro and to lower the peripheral conversion of androstenedione to estrone and to lower estrone but not estradiol levels in vivo in postmenopausal women with metastatic breast cancer. The present study was undertaken to determine the dose-response relationship of testololactone administration, to evaluate the dual effects of testololactone administration and adrenal suppression, and to examine the long-term action of the drug on endogenous estrogen levels. (16 Refs)

15. IN VIVO AND IN VITRO PHARMACOLOGICAL STUDIES OF AMINOGLUTETHIMIDE AS AN AROMATASE INHIBITOR.

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Cancer Res; 42(8,Suppl):3353s-3359s 1982

Use of steroid biosynthesis inhibitors to suppress estrogen production is a logical strategy in the treatment of women with hormone-dependent breast cancer. The clinical availability of aminoglutethimide as an inhibitor of cytochrome P-450-mediated steroid hydroxylations prompted study of the precise pharmacological and biochemical effects of this drug. Pharmacokinetic studies revealed that aminoglutethimide alters its own metabolic clearance rate as well as that of dexamethasone, a synthetic glucocorticoid. The metabolic clearance rates of other steroids such as hydrocortisone, medroxyprogesterone acetate, androstenedione, and estrone are not altered by aminoglutethimide. These findings led to development of a practical regimen of escalating aminoglutethimide dosage in combination with hydrocortisone for treatment of patients with breast carcinoma. Further studies focused upon the biochemical mechanism of estrogen suppression with aminoglutethimide. In vivo, isotopic kinetic data demonstrated that aminoglutethimide inhibits peripheral aromatase by 95 to 98% in postmenopausal women. In vitro experiments indicated that aminoglutethimide can effectively block aromatase directly in human breast tumors as well. With respect to relative potency, aminoglutethimide is a 10-fold more potent aromatase inhibitor than is testololactone but is less potent than are 4-hydroxyandrostenedione and several brominated androstenedione derivatives. Taken together, these studies suggest that aminoglutethimide blocks estrogen production at three sites in women with breast carcinoma, the adrenal cortex, extraglandular peripheral tissues containing aromatase, and breast carcinoma tissue itself. (Author abstract) (25 Refs)

16. SIGNIFICANCE OF AROMATASE ACTIVITY IN HUMAN BREAST CANCER.

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Cancer Res; 42(8,Suppl):3365s-3368s 1982

The significance of in vitro aromatization of [7alpha-3H]testosterone to estradiol by human breast cancer has been investigated by correlation with (a) estrogen receptor activity and (b) clinical response to endocrine therapy. Evidence for estradiol synthesis was obtained in 66 and estrogen receptor activity in 81 of 110 tumors. Whereas most estrogen receptor-positive tumors synthesized estradiol, the majority of receptor-negative tumors did not. This tendency for aromatization to be associated with estrogen receptor-positive tumors was statistically significant (p less than 0.005). Mean level of receptor was also significantly higher in tumors with aromatization than in tumors without estradiol synthesis (p less than 0.001). Forty patients with advanced breast cancer have been treated by endocrine therapy. There was a significant trend for tumors with aromatization to be associated with response to treatment (p less than 0.05), but the correlation was not absolute and may simply reflect the association between aromatase activity and estrogen receptors. Within the small subgroup of patients treated with aminoglutethimide or adrenalectomy, tumors with high aromatase activity responded whereas those without aromatization did not. Tumor estrogen biosynthesis may therefore be of clinical significance in selecting patients for treatments which remove sources of precursor for aromatization or inhibit aromatase activity itself. (Author abstract) (24 Refs)

17. AROMATASE IN HUMAN BREAST CARCINOMA.

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Cancer Res; 42(8,Suppl):3369s-3372s 1982

Breast carcinoma tissue is capable of forming estrogens from circulating androgen precursors. In this study, aromatase was examined in homogenates of breast adipose and breast carcinoma tissue, in normal and abnormal parenchymal breast tissue, and in breast carcinoma cells in culture. Homogenates of carcinoma tissue showed a wide range of activity in the conversion of androstenedione to estrone. The mean conversion in carcinoma tissue was greater than that seen in parenchymal tissue from patients with gynecomastia and mammary dysplasia. Homogenates of breast adipose tissue from patients with benign and malignant disorders showed comparable aromatase activity. Three cell lines isolated from a primary breast carcinoma differed in their aromatase activity demonstrating a heterogeneity of aromatase activity in cells from a single tumor. Studies of aromatase activity in breast carcinoma cells in culture over a period of 8 hr demonstrated progressive estrone formation. Testosterone formation from adrostenedione was noted in all studies using both homogenates and cell cultures. Testosterone formation from androstenedione was approximately 10-fold greater than was the formation of estrone from androstenedione in all studies. The metabolism of androstenedione to other androgens examined in homogenates of normal and carcinomatous breast tissue revealed that the major products were androsterone, 5beta-androsterone, dihydrotestosterone, and epiandrosterone. Both estrogen and androgen formation within the cell may be important in determining the cellular response. (Author abstract) (11 Refs)

18. COMPARATIVE STUDIES OF AROMATASE INHIBITORS IN RELATION TO THE SIGNIFICANCE OF ESTROGEN SYNTHESIS IN HUMAN MAMMARY TUMORS.

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Cancer Res; 42(8,Suppl):3373s-3377s 1982

The inhibitory activity of aminoglutethimide, 4-hydroxyandrostenedione, 7alpha-(4'-amino)phenylthioandrostenedione, and cyanoketone (2alpha-cyano-4,4,17alpha-trimethyl-17beta-hydroxy-5 androstene-3-one) on androgen aromatization by human mammary tumors was examined. Androstenedione and dehydroepiandrosterone were incubated with mammary tumor homogenates in the presence of a reduced nicotinamide adenine dinucleotide phosphate-generating system with or without inhibitor. All four compounds were found to be equally effective in inhibiting estrogen synthesis from dehydroepiandrosterone, but only aminoglutethimide, 4-hydroxyandrostenedione, and 7alpha(4'-amino)phenylthioandrostenedione were capable of inhibiting androstenedione aromatization. Inhibitions of androgen aromatization ranging between 81 and 97% were found and were essentially similar for both estrogen receptor-negative and estrogen receptor-positive tumors. Kinetic analysis showed 7alpha(4'-amino)phenylthioandrostenedione to be the most effective inhibitor with apparent Ki of 0.034 uM, followed by aminoglutethimide (Ki 0.26 uM) and 4-hydroxyandrostenedione (Ki 0.47 uM) using androstenedione as a substrate. These results are discussed in relation to the significance of estrogen synthesis in mammary tumors. (Author abstract) (41 Refs)

19. COMPARATIVE STUDIES OF AROMATASE INHIBITORS IN CULTURED HUMAN BREAST CANCER CELLS.

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Cancer Res; 42(8,Suppl):3378s-3381s 1982

The presence of aromatase activity, estrogen receptors, and estrogenic responsiveness in MCF-7 human breast cancer cells has allowed this cell line to be used as a unique in vitro system for investigating the biological activities of potentially therapeutic aromatase inhibitors. We now report the results of studies which have examined the cytotoxicity, antiaromatase, and intrinsic estrogenic activities of aminoglutethimide, 1,2-dehydrotestolactone (testolactone), dihydrotestosterone, 4-hydroxy-4-androstene-3,17-dione, and 10-propargylestr-4-ene-3,17-dione within MCF-7 monolayer cultures. Cell viability was determined by trypan blue exclusion, and aromatase activity was assessed by quantifying the amounts of [3H]estradiol formed from [3H]testosterone. Estrogenic activity was assessed by examining the ability of each inhibitor to increase cytoplasmic progesterone receptor and deplete cytoplasmic estrogen receptor concentrations in these cells during a 5-day incubation period. Cytoplasmic progesterone and estrogen receptors were measured by the single-saturating-dose technique using [17alpha-methyl-3H]-17alpha,21-dimethyl-19-norpregna 4,9-diene-3,20-dione and [3H]estradiol as the labeled ligands for each assay, respectively. The results showed that all of these compounds were noncytotoxic aromatase inhibitors in MCF-7 cells but that these agents demonstrated marked differences in inhibitory potency (10-propargylestr-4-ene-3,17-dione greater than 4-hydroxy-4-androstene-3,17-dione much greater than dihydrotestosterone much greater than testolactone = aminoglutethimide). The incubation of cells with 4-hydroxy-4-androstene-3,17-dione resulted in cytoplasmic progesterone and estrogen receptor responses that were similar in magnitude to those observed in other cultures incubated with equimolar concentrations of estradiol. None of the other four agents demonstrated estrogenic activity in this system. However, we have previously observed that dihydrotestosterone has substantial antiestrogenic action in this system. Taken together, these results indicate that some aromatase inhibitors may influence the hormonal regulation of human breast cancer cells by more than one mechanism. (Author abstract) (12 Refs)

20. A REASSESSMENT OF THE ROLE OF BREAST TUMOR AROMATIZATION.

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Cancer Res; 42(8,Suppl):3382s-3386s 1982

While the role of estrogens in the maintenance of human breast carcinoma has been firmly established for many yr, the sources of this estrogen remain unresolved. Input-output analysis of steroid uptake by breast carcinomas showed no specific uptake of estrogens from blood. Based on the detection of the necessary enzyme systems, Adams and Wong proposed that breast tumors could function as 'paraendocrine organs' capable of producing sufficient estradiol (E2) to stimulate their own growth. Using the reported values for the concentration of C19 steroid precursors and the rhoTTC19-E2 values one can estimate that the contribution of in situ aromatization to the tumor estrogen pool is quite small. (Author abstract) (44 Refs)

21. LUTROPIN INCREASES PHOSPHORYLATION OF A 33 000-DALTON RIBOSOMAL PROTEIN IN RAT TUMOUR LEYDIG CELLS.

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Biochem J; 204(3):809-815 1982

Localization of lutropin-dependent phosphoproteins demonstrated in tumor Leydig cells which might be involved in regulation of steroidogenesis was further investigated. Results indicated that a lutropin-dependent phosphoprotein of 33,000 dalton was present in the 40S ribosomal subunit isolated from tumor Leydig cells. Phosphorylation of the protein was stimulated by cycloheximide and puromycin, under conditions in which basal and lutropin-dependent pregnenolone productions were inhibited. The decrease with time in pregnenolone production under basal and stimulated conditions was approx the same, which suggests the possible involvement of proteins with a short half-life (approx 6 min). (20 Refs)

22. URINARY ANDROGEN METABOLITES AND RECURRENCE RATES IN EARLY BREAST CANCER.

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Eur J Cancer Clin Oncol; 18(5):447-451 1982

Androsterone and aetiocholanolone was measured in urine specimens obtained from 218 women with early breast cancer. Patients who excreted less than the median amount of these steroids had a significantly higher recurrence rate (p less than 0.005) than patients excreting more than the median value. The relationship between androgen excretion and recurrence is stronger in pre-menopausal women than in the post-menopausal group. The androgen assays are still associated with recurrence rates when patients are stratified by pathological stage, but no clear relationship was found with histological grade. (Author abstract) (23 Refs)

23. FAILURE OF HUMAN BENIGN PROSTATIC HYPERPLASIA TO AROMATISE TESTOSTERONE.

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J Steroid Biochem; 17(1):119-120 1982

Cytosol preparations of whole human prostate tissue from patients with benign prostatic hypertrophy were used to attempt demonstration of estrogen production from radiolabeled androstenedione and testosterone. While half of the testosterone was reduced to other metabolites, no aromatization of testosterone could be detected. Under the conditions used, prostatic tissues were not involved in the peripheral conversion of either androstenedione or testosterone to estrone or estradiol. (13 Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

24. URINARY UNCONJUGATED 5ALPHA-ANDROSTANE-3ALPHA, 17BETA-DIOL IN PATIENTS WITH PROSTATIC TUMOURS.

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Urol Res; 10(2):81-84 1982

A radioimmunoassay (RIA) for urinary unconjugated 5alpha-androstane-3alpha, 17beta-diol (AND) is described; the assay was applied to patients with prostatic carcinoma (PCa) and benign prostatic hypertrophy (BPH). Urine was collected from 22 normal men (25-57 yr old), 18 men with BPH (59-83 yr old), and 13 men with untreated PCa (41-79 yr old). Recovery of unconjugated AND from 3 ml urine using 2 x 4 vol diethyl ether was 80.8 +-1.5%; overall recovery for 3H-AND, including a purification step and subsequent analysis of the steroid, was 57.4 +-0.8%. Specificity of the RIA depended upon the specificity of antisera and the resolving power of thin layer chromatography in separating cross-reacting steroids. The system allowed effective separation of cross-reacting steroids from AND. The sensitivity of the assay was 79 femtomoles per assay tube. When stored at room temperature for up to 24 hr, significant changes in the level of the steroid were found. Storage at 4 C for up to 2 days and at-20 C for up to 1 yr did not significantly change the content of AND in the urine samples. Urine levels of AND in patients with BPH and in normal men were similar, while patients with PCa had significantly higher levels than either of the other groups. No relation was found between the different stages of PCa and level of AND. Thus, in patients with PCa, a considerable amount of the circulating AND is excreted by the kidneys. Measurement of AND using RIA in conjunction with plasma values could be helpful in evaluation of the biological significance of AND in PCa patients. (16 Refs)

25. VIRILIZING TUMOR OF ADRENAL CORTEX IN AN INFANT.

Bauman A, Bauman CG
Endocrine Section, Dept. Medicine, Montefiore Hosp. and Medical Center, Bronx, NY
NY State J Med; 82(7):1070-1072 1982

A virilizing tumor of the adrenal cortex is reported in an 11-mo-old female. The onset was dramatic with significant virilization occurring over a 3-wk period. Serum testosterone levels were very high (346 ng/dl) and nonsuppressible with large doses of dexamethasone. The adenoma was easily located by ultrasonography and removed without incident. Regression of masculinization occurred rapidly and follow-up 44 mo after surgery disclosed a normal 4-yr-old female. Serum testosterone levels have remained normal. (Author abstract) (16 Refs)

26. STEROID HORMONE PROFILES IN WOMEN TREATED WITH AMINOGLUTETHIMIDE FOR METASTATIC CARCINOMA OF THE BREAST.

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Cancer Res; 42(8,Suppl):3349s-3352s 1982

Recent evidence suggests that aminoglutethimide (AG), a known inhibitor of adrenal steroidogenesis, is a potent blocker of aromatase and thus of estrogen production. These properties of AG have been exploited clinicaly to reduce the biosynthesis of adrenal estrogen precursors and extraglandular estrogen production in postmenopausal women with metastatic breast carcinoma. In this study, we have explored the effects of AG on a variety of steroids, including delta(5)-C19 and -C21 compounds and delta(4)-C19 and -C21 steroids as well as plasma and urinary estrogens in a series of postmenopausal women with breast cancer treated for 2 to 26 wk. Plasma concentrations of delta(5)-C21 and -C19 compounds were reduced three-to five-fold during AG therapy and remained suppressed over the duration of the study. By contrast, the delta(4)-steroids such as progesterone, androstenedione, and 17alpha-hydroxyprogesterone rose 2-to 10-fold during the initial 2 wk of AG treatment and then fell back to starting levels or were suppressed. Plasma levels of the potent androgens testosterone and dihydrotestosterone were relatively preserved during AG therapy. The possible contribution of the postmenopausal ovary to the above hormone levels during AG therapy was examined by comparing steroid values from surgically castrated and spontaneously menopausal women. No statistically significant differences between the two groups were observed. In response to AG therapy, plasma levels of estrone and estrone sulfate were decreased 61 to 72%, and urinary estrone similarly fell 85% over the 12-wk period. Estradiol concentrations in urine and plasma were similarly reduced 40 to 66% from basal values over this same period. (Author abstract) (21 Refs)

27. THE ESTROGENIC RECEPTOR IN DESMOID TUMORS. PRELIMINARY REPORT.

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Arch Invest Med (Mex); 13(2):105-108 1982

Estrogenic hormonal receptor (ER) was studied in six patients with a histologic diagnosis of desmoid tumor. Pertinent clinical characteristics and ER levels are summarized. In five out of six patients measurable amounts of ER 4-64 femtomole(fmol)/mg protein were found and in three of the patients values were considered to be positive (greater than 10 fmol/mg protein). The levels of gonadotrophins and estradiol 17 B were normal in all patients; prolactin was discretely elevated in two patients; and in isolated patients in which growth hormone and testosterone were measured, they proved to be normal. (19 Refs)

28. URINARY OESTROGENS AND PREGNANDIOL IN BREAST CANCER PATIENTS.

Zaki K, El-Kharadly M, El-Faras A, Nour H, Kamel NI
Dept. Physiology, Medical Res. Inst., Alexandria Univ., Alexandria, Egypt
Endokrinologie; 79(1):49-56 1982

Urinary E1, E2, E3 and pregnandiol was determined in 60 premenopausal and 12 postmenopausal breast cancer patients before and after mastectomy, as well as in 30 normal females. Data obtained showed great individual variation. The general findings were low estrogens in young patients, normal in old premenopausal patients and high in post-menopausal patients. The ratio E3/E1 + E2 showed comparatively high values in premenopausal patients. Pregnandiol excretion was low in almost all premenopausal patients with the exception of few cases in the different age groups. The changes in the hormonal pattern in premenopausal breast cancer patients, before and after mastectomy, and of postmenopausal patients were discussed in view of the current literature. (Author abstract) (23 Refs)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

29. AN UPDATE ON HORMONAL RECEPTORS AND BREAST CANCER.

Eyraud JP, Martin PM, Peter J, Baudet JH
Chaire de Clinique Gynecologique et Obstetricale, Centre Hospitalier Regional et Universitaire Dupuytren, 87031 Limoges, France
Rev Fr Gynecol Obstet; 77(4):229-232 1982

Hormone receptors in breast cancer have become a major prognostic factor in combination with patient age, histological tumor grade, and the number of involved axillary ganglia. In 62% of tumors, estrogen receptors are present and functional, and 40% of tumors are positive for both estrogen and progesterone. Grade I tumors are generally more receptor positive (RP) than more advanced grades. Receptor negative tumors respond better to chemotherapy than RP tumors, and RP tumors respond to complementary hormone therapy. (12 Refs) (In FRE)

30. STEROID RECEPTORS. CLINICAL INTEREST IN CANCEROLOGY.

Rochefort H
Unite d'Endocrinologie Cellulaire et Moleculaire (U 148), INSERM, 60, rue de Navacelles et Faculte de Medecine, F 34100 Montepellier, France
Ann Pathol; 2(2):87-89 1982

The concept that the action of steroid hormones is mediated by an interaction with intracellular receptor proteins is introduced. The rationale for using estrogen and progesterone receptor determinations in the treatment of breast cancer is then discussed. Data from the literature are then described to illustrate the information given by the assay of the cytosol estrogen and progesterone receptors in human breast cancer. Even though there are some limitations, the information is very useful for predicting the hormone dependency and prognosis of breast cancer. Ideally, these assays should be performed as soon as tumor tissue is accessible to surgery before treatment. Finally, recent improvements in the assay of receptors and the use of post receptor markers such as estrogen-induced proteins are discussed. (Author abstract) (14 Refs) (In FRE)

31. PHASE II TRIAL OF TAMOXIFEN IN MALIGNANT MELANOMA.

Leichman CG, Samson MK, Baker LH
(c/o Samson) Dept. Oncology, Univ. Health Center, 4201 St. Antoine 7-C, Detroit, MI, 48201
Cancer Treat Rep; 66(6):1447 1982

A phase II clinical trial of tamoxifen (TO) in disseminated malignant melanoma with a standard dose of 10 mg TO po bid was conducted in 20 patients (9 females, 11 males, 34-81 yr old, median 51 yr). All but two patients had received previous chemotherapy or immunotherapy; most had been treated with multiple drugs, either dacarbazine alone or in combination. Disease-free interval ranged from zero (disseminated at diagnosis) to 8 yr (median, 25 mo). Median Karnofsky performance status at the time of entry into the protocol was 80 (range 40-

100). Of the 20 patients studied, 16 had predominantly soft tissue disease, 3 had lung disease, and 1 had lung and soft tissue disease. Nine patients had negative estrogen receptor protein assays, and two had 'low': 3.6 and 4.0 femtomole/10 mg wet wt of tissue. Eighteen patients were evaluable for response. One patient had a partial response after 4 wk of treatment, with regression of skin nodules. The response lasted for 3 wk prior to appearance of new disease. The estrogen receptor protein was negative in the patient. Toxic reactions were rare and consisted of mild nausea, wt gain, and hot flashes. Results of the study indicated that TO is not an effective agent in the treatment of disseminated malignant melanoma in patients who have received prior chemotherapy. (5 Refs)

32. PHASE II STUDY OF TAMOXIFEN IN PATIENTS WITH METASTATIC MALIGNANT MELANOMA.

Telhaug R, Klepp O, Bormer O
Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer Treat Rep; 66(6):1437 1982

A phase II study of tamoxifen (TAM) was conducted in 21 patients (12 males, 9 females, 29-80 yr old, median age 55 yr) with measurable disseminated malignant melanoma, and obtained results are reported to contribute to the overall estimation of the collective response rate. Tumor tissue samples for the determination of cytosol hormone receptor concentrations were obtained from seven patients prior to start of TAM therapy. Patients received TAM 40 mg/day po in two divided doses until clear evidence of tumor progression. One of the patients achieved an objective response. The patient had lung metastases that decreased greater than 50% in size after 2 mo of TAM treatment. Disease progression occurred 5 mo after the start of TAM therapy. Two patients had no change in their tumor lesions for 4 and 5 mo, respectively. In both patients, the rate of disease progression was comparatively slow both prior to and after TAM therapy. The other 18 evaluable patients showed disease progression within 2-3 mo after start of TAM therapy. None of the seven tumor tissues examined showed estradiol binding activity. No significant side effects were experienced by any of the 21 patients. Results indicated that even a 5-10% response rate could be of some clinical interest for the therapy of malignant melanoma, because the side effects of such therapy are negligible compared to those of cytotoxic drugs. (4 Refs)

33. THE SPECIFIC BINDING OF ESTRADIOL AND ESTRONE AND THE SUBSEQUENT DISTRIBUTION OF ESTROGEN-RECEPTOR COMPLEXES WITHIN MCF-7 HUMAN BREAST CANCER CELLS.

MacIndoe JH, Woods GR, Etre LA
Dept. Internal Medicine, Veterans Admin. Medical Center, Iowa City, IA, 52240
Steroids; 39(3):245-258 1982

We have examined the specific binding of estradiol (E2) and estrone (E1) within MCF-7 cells using both cytosol and whole cell suspension binding assay techniques. The results of these studies have revealed that each of these estrogens binds with high but different affinity to the same single class of cytosol receptor (ER). The incubation of intact cells with E2 at 37 C resulted in the rapid formation, nuclear binding, and nuclear processing of E2-ER complexes. Reductions of incubation temperature to 15 C and 4 C resulted in slowed but continued E2-ER formation and nuclear binding, and in a marked inhibition of nuclear receptor processing. The incubation of intact cells with E1 at 37 C also was associated with the formation, nuclear binding, and nuclear processing of estrogen-ER complexes. Interestingly, however, E2 rather than E1 represented the major species of specifically bound estrogen under these conditions. This observation suggests that the estrogenic action of E1 in MCF-7 cells may be mediated largely by the intracellular formation of E2. This phenomenon provides a likely explanation of the unexpected potency of E1 in this system previously observed by other workers. Furthermore, our results suggest that E1 may represent a major source of estrogenic stimulation for some hormone-dependent human breast tumors. (Author abstract) (7 Refs)

34. TAMOXIFEN AND AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER.

Corkery J, Leonard RC, Henderson IC, Gelman RS, Hourihan J, Ascoli DM, Salhanick HA
New England Deaconess Hosp., Boston, MA, 02115
Cancer Res; 42(8,Suppl):3409s-3414s 1982

Tamoxifen (TAM), a standard endocrine treatment for advanced breast cancer, probably acts by competing for the estrogen receptor protein in the breast tumor cells. If so, resistance to TAM may be a function of the level of the available endogenous estrogen. Inhibition of estrogen synthesis by aminoglutethimide may therefore facilitate the action of the antiestrogen. To test this hypothesis, the two agents were given concurrently (a) to patients who had become resistant to TAM and (b) to patients who had never received TAM in a randomized cross-over study against TAM alone. Patients with estrogen receptor protein-negative disease were excluded. Estrogen and aminoglutethimide levels were measured serially. In the first study, 4 of 26 patients experienced partial responses, and 4 of 26,, stabilization of their disease. In the randomized study, 4 of 11 patients on the combination and 3 of 9 of TAM alone had responses. Two patients on the combination and three on TAM alone had stabilization of disease. In the first group, the low rate of response may be attributed to extensive prior treatment. In the randomized study, there is presently no clear advantage for one treatment, and overall, there was no statistically significant correlation between degree of estrogen suppression, aminoglutethimide level, and response. The findings do not exclude the possibility that these agents may act in breast cancer by mechanisms other than inhibition of estrogen receptor. (Author abstract) (23 Refs)

35. NEW STRATEGIES FOR INVESTIGATING ANTIESTROGEN ACTION IN BREAST CANCER.

McGuire WL
Dept. Medicine/Oncology, Univ. Texas Health Science Center at San Antonio, San Antonio, TX, 78284
Cancer Res; 42(8,Suppl):3420s-3423s 1982

The major difference observed by us between estrogen and antiestrogen pathways in breast cancer cells occurs immediately after translocation. We have called the loss of nuclear receptor following estradiol administration 'processing' and have hypothesized that it is a prerequisite for estrogen stimulation in breast cancer cells and that failure of processing relates to antiestrogenic effects. In the very near future, monoclonal antibody technology could be used to dissect the processing of nuclear receptor and shed new light on the mechanism of antiestrogen action. (Author abstract) (7 Refs)

36. CONCENTRATION OF ENDOGENOUS OESTRADIOL AS RELATED TO OESTRADIOL RECEPTOR SITES IN BREAST TUMOR CYTOSOL.

Thorsen T, Tangen M, Stoa KF
Hormone Lab., Univ. Bergen Sch. Medicine, Bergen, Norway
Eur J Cancer Clin Oncol; 18(4):333-337 1982

Biopsies or mastectomy specimens from 26 malignant and 17 non-malignant human breast tumors have been examined with respect to cytoplasmic estradiol receptors and endogenous estradiol concentration. Of the malignant tumors, 45 (65%) had significant estradiol receptor concentrations (136.7 fmol/mg protein +-38.3 SEM). Estradiol values in the cytosol were not correlated to receptor levels. Cytosol estradiol concentrations in the receptor-negative tumors were normally distributed about a mean value of 7.4 fmol/mg protein +-0.9 (SEM). Estradiol levels were similar to the median concentration of receptor found in tumors from younger women, and consequently may influence receptor measurements in such tumors. In receptor-positive cytosols a much wider range (less than 1 to 69.7 fmol/mg protein) and a non-symmetrical distribution of estradiol values were found which closely corresponded to the range of occupied receptor concentrations previously measured in tumor cytosol. When tumors have undetectable estradiol values were excluded, receptor-positive cytosols had significantly higher estradiol concentrations than those found in receptor-negative tumors (p less than 0.01). No significant difference in cytosol estradiol concentration was found in receptor-positive and negative pre- and postmenopausal women. This would indicate that factors other than plasma levels influence tissue availability of estradiol. (Author abstract) (29 Refs)

37. PROGESTIN- AND ANDROGEN-BINDING COMPONENTS IN A HUMAN GRANULOSA-THECA CELL TUMOR.

Young PC, Grosfeld JL, Ehrlich CE, Roth LM
Dept. Obstetrics and Gynecology, Indiana Univ. Sch. Medicine, Indianapolis, IN, 46202
Gynecol Oncol; 13(3):309-317 1982

Macromolecules which bound progesterone (P), medroxyprogesterone acetate (MPA), and dihydrotestosterone (DHT) have been identified in the cytoplasmic fraction of a human granulosa-theca cell tumor and partially characterized. Bound [3H]P sedimented at the 3.6 S region of the sucrose gradients, whereas bound [3H]MPA was observed mainly in the 6 S region. P and MPA competed with each other for binding to these components. The specific MPA-binding sites were saturable and had a Ka of 3.6 nM-1. Heating the tumor cytosol at 37 C for 10 min diminished its progestin-binding activity. The DHT-binding components had sedimentation coefficients of 4.2 S and 6 S, and a Ka of 0.4 nM-1. They were heat sensitive and were precipitable by protamine sulfate. Attempts to demonstrate specific binding of estrogens and glucocorticoids by this tumor cytosol were unsuccessful. (Author abstract) (28 Refs)

38. TWO AIDS IN OESTROGEN RECEPTOR CHARACTERISATION.

Smyth CM, Reeve TS
Dept. Surgery, Univ. Sydney, Royal North Shore Hosp., Wallace Freeborn Professional Block, St. Leonards 2065, New South Wales, Australia
Aust NZ J Surg; 52(2):161-164 1982

Eighty three breast carcinoma primary and metastatic lesions were submitted for estrogen receptor (ER) assessment using a standard dextran coated charcoal saturation analysis (0.1 nM - 08 nM tritiated estradiol), as well as a single saturating dose (SSD) assay (8 nM tritiated estradiol). Excellent correlation between the two methods was demonstrated. The single dose assay also provided additional information to aid the construction of adequate Scatchard plots in those biopsies which exhibited high levels of specific receptor proteins. Three hundred and fifteen consecutive breast carcinoma primary or metastatic lesions, assessed for ER, had imprint cytological examinations to verify the malignancy of the specimen. Seven percent demonstrated sparse epithelial cellularity with a low or nil malignant cell proportion and showed a lower receptor positivity than the remaining specimens. (Author abstract) (10 Refs)

39. HUMAN BREAST TUMOR CYTOSOL OESTROGEN RECEPTOR BINDING TO OLIGO(DT)-CELLULOSE.

Myatt L, White JO, Fernandez MD, Burn JI
Inst. Obstetrics and Gynaecology, Hammersmith Hosp., Lonodn W12 0HS, England
Br J Cancer; 45(6):964-967 1982

The concentration of cytosol estrogen receptors and their ability to bind to oligo(dT)-cellulose was measured and correlated with the presence of nuclear estrogen receptors and cytosol progesterone receptors using 63 biopsy specimens from 61 patients (22-79 yr old; 38 postmenopausal, 23 premenopausal) with histologically confirmed primary breast carcinoma. (23 Refs)

40. 1 ALPHA,25-DIHYDROXYCHOLECALCIFEROL AND A HUMAN MYELOID LEUKAEMIA CELL LINE (HL-60). THE PRESENCE OF A CYTOSOL RECEPTOR AND INDUCTION OF DIFFERENTIATION.

Tanaka H, Abe E, Miyaura C, Kuribayashi T, Konno K, Nishii Y, Suda T
(c/o Suda) Dept. Biochemistry, Sch. Dentistry, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Biochem J; 204(3):713-719 1982

Presence of a cytosol protein specifically bound to 1alpha,25-dihidroxycholecalciferol was investigated in HL-60 cells. The active form of cholecalciferol induced differentiation of human myeloid leukemia cells and the specificity of various derivatives of cholecalciferol in inducing differentiation was well correlated with that of their association with the cytosol receptor. Results were compatible with the hypothesis the active form of cholecalciferol induces differentiation of human myeloid leukemia cells by a mechanism similar to that proposed for the classical concept of steroid hormone action. (40 Refs)

41. STEROID RECEPTORS IN NORMAL AND NEOPLASTIC FEMALE REPRODUCTIVE TISSUES.

Saarikoski S, Selander K, Kallio S, Pystynen P
Dept. Clinical Sciences, Univ. Central Hosp., Tampere, Finland
Gynecol Obstet Invest; 13(4):206-212 1982

Presence of cytosol estrogen (ER) and progestin receptors (PR) were measured in specimens of normal uterine cervix, endometrium, myometrium, Fallopian tubes, and corpora lutea, or in samples of neoplastic female reproductive tissue. ER and PR were present in all of the tissues examined except in the corpora lutea. The ratio PR/ER was higest in the endometrium and in the Fallopian tubes. No difference was found in the ER, PR, or PR/ER ratio measured from tissue samples of myometrium or myoma. The lowest PR/ER ratio of the uterus was found in the specimens from the ecto- and endocervical epithelium. (20 Refs)

42. ARE THE HISTOLOGICAL AND ULTRASTRUCTURAL FEATURES OF ENDOMETRIAL CARCINOMAS RELIABLE INDICATORS OF THEIR STEROID RECEPTOR CONTENT?

Genton CY, Buchi KA
Institut fur Pathologie der Universitat Zurich, Universitatsspital, CH-8091 Zurich, Switzerland
Gynecol Obstet Invest; 13(4):213-225 1982

Histological and ultrastructural features of endometrial carcinomas were studied in 15 postmenopausal patients to correlate the steroid receptor content with endometrial carcinoma. All but one tumor in the study contained one or both steroid receptors. Two neoplasms displayed no measurable estrogen-binding capacity but presented progesterone receptors in small amounts. In a poorly differentiated carcinoma, the high level of circulating estrogens may explain the fact that the search for estrogen receptors remained negative. In a tumor of moderate differentiation, the serum estradiol was very low suggesting that the neoplasm effectively displayed no estrogen-binding capacity. (20 Refs)

43. IDENTIFICATION OF TRANSFORMED GLUCOCORTICOID RECEPTOR FROM DEXAMETHASONE RESISTANT MELANOMA.

Hutchens TW, Hawkins EF, Markland FS
(c/o Hawkins) USC Cancer Center, Research Building One, Room 490, 1720 Zonal Ave., Los Angeles, CA, 90033
J Steroid Biochem; 16(6):705-711 1982

Transformation of the glucocorticoid receptor in RPMI 3460, clone 5 and clone 6 melanoma cells and tumors was examined using a selected chromatographic technique under various experimental conditions. Cytosolic glucocorticoid-receptor complexes from both dexamethasone-sensitive and -resistant melanoma appeared similar to previously activated glucocorticoid receptors from rat liver and kidney in being heterogeneous with respect to chromatographic properties on DEAE-cellulose. Results showed that resistance to dexamethasone-induced changes in growth observed in resistant clone 5 cells and solid tumors cannot be attributed to an inability of the receptor they contain to exist as a stable, transformed complex. (22 Refs)

44. VARIABILITY OF LEVELS OF SPECIFIC ESTROGEN BINDING IN A HUMAN ENDOMETRIAL ADENOCARCINOMA LINE.

Fridman O, Fleming H, Gurpide E
Inst. Biology and Experimental Medicine, Obligado 2490, Buenos Aires, Argentina
J Steroid Biochem; 16(5):607-612 1982

The heterogeneity of estrogen binders in cultured human endometrial adenocarcinoma cells (HEC-1B) was investigated. Specific binding of estradiol in the nuclear pellet increased when incubation temperature was raised from 4 C to 30 C, with a peak at 60 min. In contrast, specific binding in the cytoplasm declined when the temperature of incubation was raised from 4 C to 30 C. While confluent cells had very low concentrations of specific binding sites at either temperature, a sharp increase was noted during the first day of culture, at a time before cell replication began. Thereafter, levels of specific binding sites decreased inversely with increases in DNA synthesis. Most of the estradiol bound in the cytoplasm was not translocated into the nucleus. Only about 5-30% of the total (nuclear + cytoplasmic) specifically bound hormone appeared in the nucleus. These results reveal the presence in the cytoplasm of non-translocatable specific binding sites. Variable levels of specific estradiol binders can thus be seen not only in primary cultures of endometrial cells but also in cultures of an established human endometrial adenocarcinoma cell line. (9 Refs)

45. VARIATIONS IN THE LEVELS OF ESTROGEN RECEPTORS IN PROLACTIN PRODUCING PITUITARY TUMOR CELLS.

Noteboom WD, Durham JB, Mitra R
Dept. Biochemistry, Univ. Missouri Sch. Medicine, Columbia, MO, 65212
J Steroid Biochem; 16(5):633-638 1982

The binding of (3H)-17beta-estradiol in the cytoplasmic fraction of MtTW10 rat pituitary tumor cells was investigated. The capacity to bind estrogen decreased with time in culture but was not accompanied by a change in the affinity of the receptor for estrogen. When the binding of (3H)-17beta-estradiol in the 105,000 gravity cytosol of GH3 rat tumor cells was measured, the dissociation constant was found to be 2.1 X 10(-10) M and the receptor concentration was equivalent to 282 femtomoles estradiol/mg protein. Receptor concentration of the low speed supernatant of GH3 cells was 70 femtomoles estradiol/mg protein. This lower value was due to the higher amount of non-receptor protein present in this supernatant. Estrogen receptors in the MtTW10 cells were very similar to those of other rat pituitary tumors. Like normal pituitary cells, both the GH3 and the MtTW10 cells contained a receptor in the cytosol with a sedimentation constant of 8 svedberg units. Receptor could bind estrogen even in the presence of high concentrations of digitonin. The decreased binding of estradiol observed in the cytoplasmic fraction of MtTW10 cells during tumor aging was due to a decrease in the number of binding sites rather than to a change in the affinity of the receptor for estrogen. Decreased levels of receptors could be due to a decrease in the av rate of synthesis of receptors or to a complete cessation of synthesis of receptors in cells which overgrew in culture. Human pituitary tumor cells (18-54) completely lacked high affinity estrogen receptors, whether or not serum was present in the culture medium. (13 Refs)

46. QUANTITATIVE CHANGES IN ESTROGEN RECEPTOR PRODUCED BY CHRONIC DES TREATMENT OF TWO MOUSE STRAINS DIFFERING IN SUSCEPTIBILITY TO LEYDIG CELL TUMOR INDUCTION.

Terakawa N, Huseby RA, Fang SM, Samuels LT
Dept. Obstetrics and Gynecology, Osaka Univ. Medical Sch., 1-1-50 Fukushima, Fukushima-ku, Osaka, Japan
J Steroid Biochem; 16(5):643-652 1982

The effects of chronic diethylstilbestrol (DES) treatment on the estrogen receptor system in testes of BALB/c mice, which develop Leydig cell tumors after long-term DES, and C3H mice, which do not, were investigated. Estrogen receptor concentration in Leydig cell cytosols from C3H mice was similar to that observed in BALB/c mice at the beginning of DES treatment, but changed during long-term estrogenization. Estrogen receptor sites in cytosol increased significantly in BALB/c mice during DES treatment without any alteration in affinity for estrogen. A similar but lesser increase was observed in C3H mice. A single DES treatment caused an increase of nuclear receptor content in BALB/c mice which was greater than that observed in C3H mice. In C3H testes the nuclear estrogen receptor content remained constant after 7-14 days treatment while that in BALB/c mice rose to a level 150% that observed 0.75 hr after a single injection of 2.5 ug DES. These differences in nuclear receptors parallel differences in both early induction of DNA synthesis in Leydig cells and the induction of Leydig cell tumors observed in the two strains. (26 Refs)

47. GLUCOCORTICOIDS AND MELANOMA: RECEPTOR PROPERTIES OF DEXAMETHASONE SENSITIVE AND RESISTANT TUMORS.

Hawkins EF, Hutchens TW, Fligiel S, Horn D, Markland FS
Univ. Southern California Cancer Center, Building 1, 1720 Zonal Ave., Los Angeles, CA, 90033

J Steroid Biochem; 16(5):673-681 1982

Solid tumors were grown in hamsters with the use of dexamethasone (DEX)-sensitive (clone 6) and -resistant (clone 5) cells cloned from RPMI 3460 Syrian hamster melanoma. Studies are reported on the comparative characteristics of these tumors including their in vivo growth responses to DEX, their histology and some physicochemical properties of their cytosolic glucocorticoid receptors. Growth of tumors from DEX-sensitive cells was retarded by daily injection of DEX into the animals. Both tumor types contained cytosolic glucocorticoid receptors (which were significantly higher in clone 5 tumors), and had similar affinity and steroid specificity characteristics which enable them to exist as stable, activated (nuclear binding) complexes. Some physicochemical differences were found. Sucrose gradient analysis indicated cytosols from both tumors contained 7S receptor complexes but clone 6 contained an additional 13S form. Activated receptors isolated by diethylaminoethanol (DEAE)-cellulose chromatography from both clone 5 and 6 tumor cytosols sedimented as a single peak at 4-5S. The DEAE-cellulose profiles indicate that only the clone 6 activated complex (Peak I) was heterogeneous with respect to charge. DNA-cellulose chromatography indicated that activated receptor from clone 5 tumor cytosols may bind more tightly to DNA than those from clone 6. (21 Refs)

48. CYTOPLASMIC RECEPTORS OF STEROID HORMONES IN PRIMARY BREAST TUMOR.

Bassalyk LS, Murav'eva NI, Smirnova KD, Kuz'mina ZV, Vishniakova VV, Ermilova VD
Center Oncology Res. USSR Acad. Medical Sciences, Moscow, USSR

Vopr Onkol; 28(4):6-10 1982

Receptors of steroid hormones (estrogens, progesterone and glucocorticoids) were studied in 148 patients with primary tumors of the mammary gland at different stages. All three types of receptors were found in 40% of patients. Receptor levels were compared vs menstrual status, histological pattern of tumor and preliminary chemo-hormonotherapy. It was established that estrogen and progesterone levels depend on menstrual status. No significant correlation was found between the degree of tumor cell differentiation and level of estrogen receptors. A retrospective assessment of estrogen receptor level and chemo-hormonotherapy results in 74 premenopausal patients with Stage II tumor is given. (Author abstract) (10 Refs) (In RUS)

49. CORRELATIONS OF THE RECEPTOR CONTENT AND ULTRASTRUCTURE OF BREAST CANCER CELLS.

Tulusan AH, Hamann M, Prestele H, Ramming I, Von Maillot K, Egger H
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 23, D-8520 Erlangen, W. Germany

Arch Gynecol; 231(3):177-184 1982

Ultrastructure of breast cancer cells in relation to estrogen receptor (ER) status was studied in tissue from 127 breast cancers (112 primary tumors, 6 recurrent lesions, 9 metastases). ERs were detected in 78% of the lesions. The proportion of cancers positive for ERs was slightly higher with histological malignancy Grades I and II, and in nuclear malignancy Grades 1, 2, and 3, than in histological malignancy Grade II and nuclear malignancy Grade 4. With classification by electron microscopy, the proportion of ER-positive cancers was significantly higher in cancers with well-differentiated cytoplasm than in cancers with poorly-differentiated cytoplasm, irrespective of grade of malignancy, and in both primary solid breast cancer and cancers in postmenopausal women. Fifty-two of 113 cancers were positive for progesterone receptors. Cancers positive for progesterone receptors were generally of low histological and low nuclear malignancy. Differentiation of the cancer cells seems to be more important than histology or nuclear malignancy grading in relation to receptor content. (16 Refs)

50. PROGNOSTIC SIGNIFICANCE OF THE STEROID RECEPTOR CONTENT IN PRIMARY BREAST CANCER.

von Maillot K, Horke W, Prestele H
Frauenklinik der Universitat Erlangen-Nurnberg, Universitatsstr. 21/23, D-8520 Erlangen, W. Germany

Arch Gynecol; 231(3):185-190 1982

Estrogen receptor (ER) and progesterone receptor (PR) contents in the primary tumor, involvement of axillary lymph nodes, and menopausal status were studied in relation to recurrence and survival rates in 222 patients with primary breast cancer. Women whose primary tumor showed no ERs or PRs developed recurrent disease earlier, and in the first 5 yr, more frequently. With a median period of observation of 46 mo, the recurrence rate for ER-positive cases (36%) was about equal to that for ER-negative cases (39%), but the free interval (time between mastectomy and appearance of recurrence) was markedly shorter for patients with receptor-negative tumors. Even after 6.5 yr, the survival rate for patients with ER-positive tumors was better than for those with ER-negative tumors; a similar trend seemed apparent in relation to PRs. Survival and recurrence rates seem to be more favorable for patients with estrogen receptor-positive breast cancer. This expectation applies only for patients who receive no further treatment or who continue on a given therapy. (14 Refs)

51. FORMATION OF DUCT-ALVEOLAR STRUCTURES AND NEW TYPES OF TUMORS BY A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) IN VIRGIN MICE.

Matsuzawa A, Kaneko T, Ikeda Y, Yamamoto T
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Gan; 73(3):372-376 1982

TPDMT-4 tumors showed significant growth in pregnant mice but not in virgins. Tumor pieces at transplant generation 14 were implanted into the gland-free (right) and the intact (left) fat pads in virgin mice and followed over a 1-yr period. The transplants formed outgrowths similar to normal mammary glands in the cleared fat pads. The outgrowths were hyperactive when compared with host glands and varied from one mouse to another in extent of development. In contrast, they did not outgrow and remained as traces among host glands in the intact fat pads. Tumors developed 41 and 32 wk after implantation in the right and the left pads, respectively, in one of 18 mice. The tumor from the cleared fat pad was an ovarian-sensitive pale cell carcinoma, and contained estrogen receptors (ER) but not progesterone receptors (PR). That from the intact fat pad was a type B carcinoma which was ovarian-dependent and contained both ER and PR at levels comparable to those of the parent tumor. (Author abstract) (16 Refs)

52. SEX STEROID RECEPTORS IN DIVERSE HUMAN TUMORS.

Kobayashi S, Mizuno T, Tobioka N, Ichimura H, Samoto T, Tanaka H, Masaoka A, Wakabayashi S, Umemura S, Fukuoka H, Nagai H
Second Dept. Surgery, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 73(3):439-445 1982

The estrogen receptor was assayed in 8 intracranial meningiomas, 14 lung cancers, 3 thymomas and 2 malignant lymphomas using the dextran-charcoal method. Progesterone and androgen receptors were also assayed in all the cases of lung cancer. The estrogen receptor assay was positive in three meningiomas, two lung cancers, and all thymomas and malignant lymphomas. The androgen receptor assay was positive in one case of lung cancer but the progesterone receptor was negative in all assayed cases. No cases showed multiple receptor positivity. An antiestrogen (tamoxifen) was administered to one case each of intracranial meningioma and lung cancer with positive estrogen receptor. The receptor content was decreased to an undetectable level in the former after 4 mo of administration. This finding suggests the estrogen dependency of the tumor. The lung cancer patient, however, died 2 wk later without any evidence of hormone dependency. (Author abstract) (27 Refs)

53. RADIOTRACERS BINDING TO ESTROGEN RECEPTORS: I: TISSUE DISTRIBUTION OF 17 ALPHA-ETHYNYLESTRADIOL AND MOXESTROL IN NORMAL AND TUMOR-BEARING RATS.

Feenstra A, Nolten GM, Vaalburg W, Reiffers S, Woldring MG
(c/o Vaalburg) Dept. Nuclear Medicine, Univ. Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands
J Nucl Med; 23(7):599-605 1982

Ethynylestradiol and moxestrol can be labeled with carbon-11 by introducing this positron emitter in the 17alpha-ethynyl group. To investigate their potential as radiotracers binding to estrogen receptors, we studied the tissue distribution of tritiated ethynylestradiol and moxestrol, with specific activities of 57 Ci/mmol and 77-90 Ci/mmol, respectively, in the adult female rat. At 30 min after injection, both compounds showed specific uptake in the uterus (% dose/g): 2.52 for ethynylestradiol and of 2.43 for moxestrol. A decrease of the specific activity to 6-9 Ci/mmol resulted in uterine uptakes of 1.60 and 2.10 respectively, for ethynylestradiol and moxestrol, at 30 min. In the female rat bearing DMBA-induced mammary tumors, specific uptake was also measured in the tumors, although the values were only 25-30% of the uterine uptake. Moxestrol showed a greater uptake selectivity in the tumors compared with ethynylestradiol. From this study we conclude that ethynylestradiol and moxestrol have good potential as tracers binding to mammary tumors that contain estrogen receptors. (Author abstract) (24 Refs)

54. N,N'-DIALKYL-1,2-BIS(HYDROXYPHENYL)ETHYLENEDIAMINES AND N,N'-DIALKYL-4,5-BIS(4-HYDROXYPHENYL)IMIDAZOLIDINES: SYNTHESES AND EVALUATION OF THEIR MAMMARY TUMOR INHIBITING ACTIVITY.

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J Med Chem; 25(7):832-837 1982

Diastereomeric N,N'-dialkyl-1,2-bis(hydroxyphenyl)ethylenediamines (5) were synthesized and tested for their affinity for the estradiol receptor. Only the (+-)-1,2-bis(4-hydroxyphenyl)ethylenediamines with the alkyl groups C3H7 [(+-)-5c, Ka = 1.1 x 10(6)], C4H9 [(+-)-5e, Ka = 3.6 x 10(6)], and C5H11 [(+-)-5h, Ka = 2.2 x 10(6)] showed a marked affinity, which is mainly due to the (+) enantiomers [eg, (+)-5e, Ka = 2.1 x 10(7)]. No enhancement of affinity by cyclization to imidazolidines [eg, (+-)-trans-7a, Ka = 1.2 x 10(7)] was observed. These compounds [eg, (+-)-, (+)-, and (-)-5e], which did not produce any uterine response in the mouse, were able to inhibit weakly the growth of the DMBA-induced mammary carcinoma of the rat. The inhibitory effect of (+-)-5e against MCF-7 cells, which can be overcome by hexestrol, makes a direct antiestrogenic mode of action probable, since general cytotoxic effects and a central action could be ruled out. (Author abstract) (27 Refs)

55. TAMOXIFEN THERAPY FOR ADVANCED OVARIAN CANCER.

Schwartz PE, Keating G, MacLusky N, Naftolin F, Eisenfeld A
Dept. Obstetrics and Gynecology, Yale Univ. Sch. Medicine, 333 Cedar St., P.O. Box 3333, New Haven, CT, 06510
Obstet Gynecol; 59(5):583-588 1982

Thirteen patients with rapidly advancing recurrent epithelial ovarian cancers, in whom chemotherapy and, in some cases, radiation therapy failed, were treated with the estrogen antagonist tamoxifen. The presence of cytosol estrogen receptors, which have recently been identified in ovarian cancer specimens, was determined in the tumor from each patient prior to tamoxifen treatment. No complete responses were observed. One patient had a partial response and 4 patients had prolonged stabilization of disease. All patients with stabilized disease had estrogen receptor levels that were borderline or high. Eight patients demonstrated no response to oral tamoxifen therapy, but 5 of these had partial small bowel obstruction secondary to advanced recurrent cancer. As tamoxifen in this preliminary study may have stabilized rapidly advancing recurrent ovarian cancer, its role in the primary treatment of ovarian cancer in combination with cytotoxic chemotherapy should be considered. (Author abstract) (23 Refs)

56. STEROID HORMONE RECEPTORS IN THE RAT MAMMARY ADENOCARCINOMA INDUCED BY N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Li SA, Malejka-Giganti D, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
JNCI; 69(1):41-45 1982

The steroid hormone receptors in N-2-fluorenylacetamide (2-FAA)- and N-hydroxy-2-FAA-induced mammary adenocarcinomas in outbred Sprague-Dawley rats were analyzed. Both 8S and 4S estrogen-binding components have been detected in cytosols of these tumors following sucrose gradient sedimentation in low salt. Competitive binding analyses of this binder indicated a specificity profile expected of an estrogen receptor. Both androgen and progesterone receptors were also present in the cytosols of these mammary tumors. While the androgen receptor sedimented in the 8S region of the gradient, the progestin binder appeared only as a 4S moiety under similar conditions. The relative concentrations of these receptors (expressed in fmol/mg protein +- SE) were: 17 beta-estradiol (28.6 +-4.1) greater than 5alpha-dihydrotestosterone (8.5 +-2.2) greater than progesterone (5.0 +-1.3). The progesterone receptor was increased at least eightfold in the mammary adenocarcinomas from ovariectomized rats that were treated with diethylstilbestrol for 6 days. Binding equilibrium data indicated K = 1.2-1.8 x 10(9) M-1 for the above cytoplasmic hormone receptor complexes (Ka, association constant). Although cytosols prepared from lactating mammary gland contained appreciable quantities of glucocorticoid receptor, only trace amounts were found in the mammary adenocarcinoma. (Author abstract) (33 Refs)

57. ANTIANDROGENIC ACTIVITY OF HORMONAL THERAPY IN HUMAN PROSTATIC CANCER (MEETING ABSTRACT).

Tomera KM, Benson RC, Veneziale CM
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We studied the competition of diethylstilbestrol (DES), diethylstilbestrol diphosphate (STILPHOSTROL), 17 beta-estradiol, megestrol acetate (MEGACE), chlorotrianisene (TACE), and estramustine (the dephosphorylated form of ESTRACYT), for both cytosolic and nuclear androgen receptor in surgically extirpated specimens. There were 25 primary and 5 metastatic untreated prostatic adenocarcinoma tumors. Six point dextran coated charcoal assays were analyzed by Scatchard plots utilizing R-1881 as the ligand and a 1000 fold excess of triamcinolone acetonide to block the progesterone receptor. DES, STILPHOSTROL, TACE, ESTRACYT, and estramustine showed little or no inhibition of receptor binding. MEGACE and 17 beta-estradiol inhibited both the cytosolic and nuclear androgen receptor binding. Antiandrogenic activity or inhibition did not correlate with levels of receptor, affinity constants, stage or grade of tumor, and inhibitions of the metastatic lesions were the same as their primary. 17 beta-Estradiol appears to have a theoretical advantage in the treatment of prostate cancer because of its dual effect of estrogenic pituitary suppression and its direct cellular androgenic inhibition. (no Refs)

58. VARIOUS CHARACTERISTICS OF HORMONE-INDEPENDENCY IN BREAST CANCER (MEETING ABSTRACT).

Kiang DT, Handschin B
Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, 55455
Proc Am Assoc Cancer Res; 23:185 1982

Following serial transplantation, GR mouse mammary tumors transit from hormone-dependent (HD) to -independent (HI). Our previous report indicated that 1) cyclic resurge of progesterone receptor (PgR) occurred every 4-6 generations, even tumors remaining in HI status, and 2) HI tumors in late transplant generations retain low receptor levels. Current study is to assess any qualitative modulation in ER (estrogen receptor) between HD and HI tumors by using IEF (isoelectric focusing) technique, Scatchard plot and by measuring the ability of cytosol-nuclear translocation of receptor-steroid complexes. Four independently developed GR mouse mammary tumor series were used; A, D, E, and F in various transplant generations (generation number in parentheses). Tumors of A(1) through A(4), E(2) and F(2) were HD; while A(5) through A(22) and D(1) were HI. IEF gel analysis revealed a similar single pH 4-5 band in either A(22) HI tumor or E(2) and F(2) HD tumors. During serial transplantations from A(5) through A(13), the quantity of cytosol receptor decreased, while the steroid receptor affinity, Ka steadily increased from 2.2 to 6.5 x 10(9)/M. D(1) tumors had no detectable cytosol ER and PgR. However, translocation studies revealed that their nuclei had the capability to retain preformed receptor-estradiol complexes. On the contrary, nuclei of A(11) tumors, also HI tumors derived from an initially HD tumor, lost this nuclear binding function. (1 Ref)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

59. ANDROGENOTHERAPY OF DYSMYELOPOIETIC SYNDROME.

Mitsutani S, Hiraide S
Dept. Internal Medicine, Shinko Hosp., Kobe, Japan
Rinsho Ketsueki; 23(1):12-19 1982

Five patients with dysmyelopoietic syndrome (DMPS) are reported. In one patient, a 70-yr-old woman, DMPS was observed prior to death due to acute myelomonocytic leukemia. Androgenotherapy was used successfully against DMPS associated anemia that was due to dyserythropoiesis in four of the patients. Further research was thought to be necessary to ascertain the potential of the drugs used to hasten the progression of DMPS into leukemia. (31 Refs) (In JPN)

60. BCG INDUCED MURINE PERITONEAL EXUDATE CELLS: CYTOTOXIC ACTIVITY AGAINST A SYNGENEIC BLADDER TUMOR CELL LINE.

Pang AS, Morales A
(c/o Morales) Dept. Urology, Queen's Univ., Kingston General Hosp., Kingston, Ontario K7L 2V7, Canada
J Urol; 127(6):1225-1229 1982

Peritoneal exudate cells from mice after intraperitoneal injection of 10 mg of BCG demonstrated cytolytic activity in vitro against the syngeneic bladder tumor cell line MBT-2. The cytolytic effector cells are nonadherent, nonphagocytic and trypsin resistant. Moreover these cells are cyclophosphamide and hydrocortisone sensitive. It is suggested that an NK-like cell constitutes the major, if not all the population of effector cells in this reaction. (Author abstract) (33 Refs)

61. PREVENTION OF PLATELET AGGREGATION IN PATIENTS WITH PROSTATIC CANCER DURING ESTROGEN THERAPY.

Koiso K, Akima H, Niijima T
7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
Urology; 19(6):579-583 1982

In prostatic cancer patients treated with synthetic estrogen, hexestrol, increased levels of platelet aggregation were observed in accordance with a significant decrease of platelet cyclic AMP. Dipyridamole, which is known to inhibit phosphodiesterase activity, was used to prevent this platelet aggregating effect of hexestrol. Inhibitory effect of dipyridamole on platelet aggregation was demonstrated in patients treated with hexestrol during 1 yr of observation. (Author abstract) (18 Refs)

62. MORPHOLOGICAL AND NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO FIBROBLASTS BY DIETHYLSTILBESTROL AND ITS ANALOGS.

McLachlan JA, Wong A, Degen GH, Barrett JC
Transplacental Toxicology Section, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3040-3045 1982

A mammalian cell culture system using normal, diploid Syrian hamster embryo fibroblasts was used as a model to study the ability of diethylstilbestrol (DES) and related compounds to induce neoplastic transformation. Like benzo(a)pyrene, a known chemical carcinogen, DES (0.01 to 10 ug/ml) induces morphological transformation of Syrian hamster embryo fibroblasts in vitro; the transformed colonies were indistinguishable from colonies of benzo(a)pyrene-transformed cells. The morphologically transformed colonies derived from either benzo(a)pyrene- or DES-treated cells were tumorigenic when injected into newborn hamsters. At doses of 0.01 to 1 ug/ml for 48 hr, DES did not inhibit or stimulate cell proliferation. Structural analogous of DES were also tested in the Syrian hamster embryo transformation system. Like DES, tetrafluoro-diethylstilbestrol, dimethylstilbestrol, and cis,cis-dienestrolmorphologically transformed Syrian hamster embryo cells. The transformation frequency of dimethylstilbestrol was much less than that of DES, tetrafluorodiethylstilbestrol, or cis,cis-dienestrol. Hexestrol, dimethoxydiethylstilbestrol, and trans,trans-dienestrol did not transform these cells. No correlation could be demonstrated between reported estrogenic potency of the compounds and their cell-transforming capacity. Structure-activity relationships developed for these chemicals suggest that metabolism via specific pathways plays a role in DES-induced cell transformation. (Author abstract) (33 Refs)

63. UNUSUAL ANDROGEN SENSITIVITY OF THE ANDROGEN-INDEPENDENT DUNNING R-3327-G RAT PROSTATIC ADENOCARCINOMA: ANDROGEN EFFECT ON TUMOR CELL LOSS.

Humphries JE, Isaacs JT
(c/o Isaacs), Johns Hopkins Oncology Center, Baltimore, MD, 21205
Cancer Res; 42(8):3148-3156 1982

Shessel et al have reported previously that the serially transplantable Dunning R-3327-G rat prostatic adenocarcinoma grows faster in intact vs castrated male rats. The present study has demonstrated that this is because the G tumor is composed of androgen-independent but -sensitive prostatic cancer cells. The conclusion that G tumor cells are androgen independent is based upon the observations that these cells are capable of growing following inoculation into castrated male rats and that castration of intact male rats bearing established G tumors induces neither regression of tumor volume nor cessation of the continuous growth of the tumor. The G tumor cells, while being androgen independent are, however, highly sensitive to androgen for their maximal rate of tumor growth. This androgen sensitivity is demonstrated by the fact that the G tumor cells can be reversibly shifted to a faster or slower growth rate simply by manipulation of the host androgen status. The androgen sensitivity of G tumor growth rate is unusual in that it is not due to androgenic stimulation of cell division but to androgen-induced inhibition of G tumor cell loss (ie, the rate of G tumor cell loss is reduced by over 50% when androgen is present). The androgen sensitivity of G tumor cell loss is also unusual in that, due to the low level of 5 alpha-reductase activity of the G tumor, the predominant intracellular androgen responsible for this inhibition is untreated intact hosts appears to be testosterone and not dihydrotestosterone (DHT). In castrated rats, however, exogenous treatment with DHT is equally as effective as exogenous testosterone in inhibiting G tumor cell loss. These results suggest that G tumor cells are sensitive to either testosterone or DHT but that in untreated intact hosts little DHT is formed by the tumor cells. (Author abstract) (15 Refs)

64. GROWTH OF NORMAL HEMOPOIETIC CELLS IN CULTURES OF BONE MARROW FROM LEUKEMIC MICE.

Hays EF, Hale L
Dept. Medicine, Sch. Medicine, Univ. California Los Angeles, 405 Hilgard Ave., Los Angeles, CA, 90024
Eur J Cancer Clin Oncol; 18(4):413-418 1982

Bone marrow from mice with spontaneous leukemia was studied in long-term culture in the presence of 10(-7) M hydrocortisone. These conditions resulted in a complete loss of leukemia cells from marrows which initially showed 95% or greater replacement with lymphoblasts. The culture conditions were also found to favor the growth of hemopoietic stem cells and the surviving cultured cells produced sufficient numbers of these cells to protect lethally irradiated (950 rads) syngeneic mice. The irradiated recipients of the cultured marrow did not develop leukemia during the 180 days of observation post-irradiation, indicating the absence of leukemia cells in the inocula. A loss of leukemia cells in vitro occurred in cultures with and without the addition of hydrocortisone to the medium. Hydrocortisone was shown to have a stimulating effect on maintenance of hemopoietic stem cells, granulocyte progenitors and granulopoiesis in these cultures. (Author abstract) (12 Refs)

65. DISTINCT SIGNALS FOR ANTIBODY-DEPENDENT AND NONSPECIFIC KILLING OF TUMOR TARGETS MEDIATED BY MACROPHAGES.

Ralph P, Williams N, Nakoinz I, Jackson H, Watson JD
Dept. Developmental Hematopoiesis, Memorial Sloan-Kettering Cancer Center, Rye, NY, 10580
J Immunol; 129(1):427-432 1982

Conditions influencing the generation of antibody-dependent cellular cytotoxicity (ADCC) and several types of nonspecific tumor cell killing by macrophages were compared. Resident mouse peritoneal macrophages and several macrophage cell lines spontaneously display very low levels of ADCC to lymphoma targets. However, ADCC could be greatly stimulated in these macrophage populations by several days of culture with lipopolysaccharide (LPS), tumor promoter phorbol myristic acetate (PMA), and lymphokine (LK) preparations. Fibroblast L cell-conditioned medium (L-CM), a source of activities required for in vitro macrophage colony formation, also augmented ADCC. Two days of preincubation was optimal for stimulation of this cytotoxic activity. In contrast to these results, pretreatment of macrophages with any of the agents inhibitor tumor toxicity induced by nonspecific activating drugs present during the assay. This inverse relation between ADCC and nonspecific killing after pretreatment was obtained with peritoneal cells and two cloned macrophage cell lines. Thus, although the same cell or cell type can mediate both types of killing, the two mechanisms seem to be mediated by distinct states of a macrophage. The ADCC-stimulating agents, LPS, LK, and L-CM, probably have a common pathway of activation, because dexamethasone at 10(-6) M inhibited their effect. The factors in the LK and L-CM that stimulate ADCC are distinct from LPS, because the endogenous activities were inactivated by boiling. The activities are also separate from interleukin 2 and myeloid colony-stimulating factor purified from L-CM, CSF-1, had no effect on macrophage tumoricidal activity. ADCC-stimulating activity was not the same as macrophage-activating factor for nonspecific killing of fibrosarcoma targets, because the latter is not found in L-CM. It is concluded that macrophage ADCC and nonspecific cytotoxicity may be regulated by different endogenous signal and may represent different states of stimulated macrophages. (Author abstract) (41 Refs)

66. ACTIVATION OF LYSOSOMAL ENZYMES AND TUMOUR REGRESSION CAUSED BY IRRADIATION AND STEROID HORMONES.

Ball A, Barratt GM, Wills ED
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Eur J Cancer Clin Oncol; 18(5):489-494 1982

The lysosomal enzyme activity and membrane permeability of mouse C3H mammary tumors has been studied using quantitative cytochemical methods following irradiation of the tumors with doses of 1,500, 3,500 or 6,000 rad gamma rays. No change in the lysosomal enzyme activity was observed immediately after irradiation, but increased enzyme activity and increased membrane permeability were observed 24 hr after irradiation with doses of 3,500 or 6,000 rad. Twenty-four hr after injection of prednisolone there was a marked increase of lysosomal membrane permeability and enzyme activity, and injection of prednisolone soon after irradiation enhanced the effect of irradiation. After a dose of 6,000 rad and prednisolone, the lysosomal membrane permeability increased to 191% of the control and the enzyme activity to 326% of the value of the control tumors. Measurement of tumor size after irradiation or after a combined treatment with irradiation and prednisolone showed that a close correlation exists between tumor regression and lysosomal enzyme activity. The experiments support the view that lysosomal enzymes play an important role in tumor regression following irradiation. (Author abstract) (12 Refs)

67. ESTABLISHMENT OF GONADOTROPIN-RESPONSIVE MURINE LEYDIG TUMOR CELL LINE.

Rebois RV
Membrane Biochemistry Section, Developmental Metabolic Neurology Branch, National Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
J Cell Biol; 94(1):70-76 1982

Several clonal Leydig tumor cell lines have been established by adapting the transplantable Leydig tumor, M548OP, to culture. One of these cell lines, MLTC-1, has been characterized with regard to the gonadotropin-responsive adenylate cyclase system. The binding of 125I-labeled human chorionic gonadotropin (hCG) was blocked by excess unlabeled hCG and lutropin (LH) but not by follitropin, thyrotropin, or insulin, indicating the presence of specific receptors for hCG and LH. Based on the specific binding of hCG to isolated MLTC-1 membranes, the calculated dissociation constant was 1.0 +-0.2 x 10(-10) M. The receptors appeared identical to those from normal murine Leydig cells when analyzed by SDS PAGE and sucrose density gradient centrifugation. The molecular wt and sedimentation coefficient were 95,000 daltons and 8.5 S, respectively. MLTC-1 cells responded to hCG by accumulating cyclic AMP and producing progesterone. Cyclic AMP accumulation was time- and dose-dependent with a maximal accumulation occurring at approx 0.2 nM hCG. At saturating levels of hCG, cAMP levels reached a max by 30 min and then declined very slowly. Adenylate cyclase activity in membranes prepared from MLTC-1 cells was stimulated by hCG, LH, NaF, cholera toxin, and guanyl-5'-ylimidodiphosphate. Additionally, choleragen was found to ADP-ribosylate a membrane protein of 54,000 daltons. This protein resembles the proposed guanine nucleotide regulatory component in both size and choleragen-dependent reactivity. These data suggest that MLTC-1 cells possess a gonadotropin-responsive adenylate cyclase system consisting of a specific hormone receptor, a regulatory component, and a catalytic subunit. (Author abstract) (40 Refs)

68. CELL COMPETENCE FOR INDUCTION OF DIFFERENTIATION BY INSULIN AND OTHER COMPOUNDS IN MYELOID LEUKEMIC CLONES CONTINUOUSLY CULTURED IN SERUM-FREE MEDIUM.

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Blood; 60(1):208-212 1982

Clones of myeloid leukemic cells varying in their competence for induction of differentiation have been continuously grown in serum-free medium. In the medium used, which contained transferrin, the growth rates of these cells were nearly similar to those found in serum-containing medium. The clones also maintained in this medium their competence for induction of differentiation by the normal macrophage and granulocyte differentiation-inducing protein MGI-2, the steroid dexamethasone, and lipopolysaccharide. In contrast to the results with these inducers, some clones continuously cultured in a serum-free medium showed a gain of inducibility by insulin and another clone a gain of inducibility by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate in low serum and serum-free medium. Induction of differentiation by these two compounds was therefore inhibited in these clones by the presence of serum. It is suggested that serum-free medium may also show the existence of other inducers of differentiation not detected in serum-containing medium and that these results are relevant to the possible therapeutic use of compounds such as insulin for the induction of normal differentiation in leukemic cells in vivo. (Author abstract) (24 Refs)

69. MORPHOLOGICAL AND PROLIFERATIVE CHARACTERISTICS OF HUMAN BREAST TUMOR CELLS CULTURED ON PLASTIC AND IN COLLAGEN MATRIX.

Leung CK, Shiu RP
(c/o Shiu) Dept. Physiology, Univ. Manitoba, Winnipeg, Manitoba R3E 0W3, Canada
In Vitro; 18(5):476-482 1982

Collagen, a major component of the extracellular matrix, is important in maintaining the in vivo characteristics of epidermal cells in vitro. In the present study, the morphological and proliferative characteristics of two human mammary epithelial cell lines (T-47D and MCG-7) cultured in cowhide collagen (Vitrogen 100) were studied. When grown in collagen, the tumor cells displayed a spherical shape and formed multilayered, tumorlike aggregates; desmosomes were observed between cells. In contrast, both cell lines grew as monolayers on plastic substratum; cells were characteristically flat and polygonal. When grown in collagen matrix, the human breast cancer cells became more dependent on serum for growth: cells proliferated in the presence of 10% fetal bovine serum (FBS) but failed to grow in 1% serum. On the other hand, these cells proliferated rapidly in 1% serum when they were grown on plastic. Even in 10% serum the doubling time of cells cultured in collagen was longer than that of cells maintained on plastic. In addition, cells cultured in collagen proliferated rapidly in a serum-free medium containing insulin, epidermal growth factor (EGF), estrogen, and transferrin. The collagen gel system may be useful for characterizing physiologically important trophic factors that regulate the proliferation and other functions of human breast tumor cells. (Author abstract) (19 Refs)

70. ESTROGENS STIMULATE CELL PROLIFERATION AND INDUCE SECRETORY PROTEINS IN A HUMAN BREAST CANCER CELL LINE (T47D).

Chalbos D, Vignon F, Keydar I, Rochefort H
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J Clin Endocrinol Metab; 55(2):276-283 1982

The effects of estradiol (E2) on two cloned sublines derived from the T47D human breast cancer cell line have been studied in vitro. Cell proliferation was evaluated by DNA assay, cell counts, and thymidine incorporation. The rate of synthesis of proteins released into the cell culture medium was assayed by [35S]methionine incorporation and polyacrylamide gel electrophoresis, followed by fluorography. In clone 11, which contains estrogen and progesterone receptors, estradiol (1 pM-1 nM) stimulated cell proliferation 2-to 5-fold after a lag period of 6 days. Maximal stimulation was observed with 1% of 3% fetal calf serum and without added insulin. The effect of E2 was biphasic, since the growth rate was stimulated for E2 concentrations less than 10 nM and then progressively inhibited for higher concentrations. Dexamethasone, dihydrotestosterone, progesterone, and R5020 (at 1 nM or 1 uM) did not modify cell growth. The antiestrogen Tamoxifen (1 uM) inhibited the E2-induced stimulation and decreased the growth of control cells. Estrogen also stimulated 2-to 3-fold the synthesis of approximately 60K mol wt dalton proteins which were released into the medium. This effect was seen as early as 1 day of E2 treatment, and a plateau of stimulation was reached with 0.1 nM E2. By contrast, in clone 8, which contains low concentrations of estrogen and progesterone receptors. E2 had no effect on cell growth and stimulated slightly the synthesis of a 55K protein. These results demonstrate that E2 is able to directly stimulate the proliferation of human epithelial breast cancer cells after having stimulated the synthesis of approximately 60,000 dalton proteins released into the medium. (Author abstract) (30 Refs)

71. RESPONSE OF VASCULAR PERMEABILITY IN INTRAHEPATIC TUMORS TO STEROIDAL AND NON-STEROIDAL ANTI-INFLAMMATORY AGENTS (MEETING ABSTRACT).

Ackerman NB, Makohon S
Upstate Medical Center, Syracuse, NY, 13210
Proc Am Assoc Cancer Res; 23:167 1982

Previous studies in this laboratory have demonstrated increased vascular permeability in Walker carcinosarcomas implanted within the liver of Sprague-Dawley rats compared to permeability in the host liver tissue. The present studies were designed to determine whether the tumor vasculature will respond to the anti-inflammatory effects of steroids and non-steroidal agents with measurable decreases in permeability. All drugs were injected in a bolus directly into the celiac artery, followed by intravenous administration of Evans blue. Rats were sacrificed at 5 min, 30min and 6 hours and dye was extracted from tumor and liver samples. Permeability activity was determined by spectrophotometric measurement. All steroids tested (hydrocortisone, methyl-prednisolone, and triamcinolone) significantly decreased tumor vascular permeability at all time periods liver vascular permeability was more variably affected by these drugs. Non-steroidal agents (indomethacin, phenylbutazone, ibuprofen and naproxan) produced similar effects on tumors; naproxan also appeared to decrease hepatic vascular permeability. Epinephrine lowered tumor vascular permeability without affecting the liver. Vascular permeability of newly formed tumor vessels resembles that within inflammatory tissues, and increases only with physical changes produced by extreme hypothermia and hyperthermia, but does not respond further to agents such as histamine. The tumor vessels appear to respond to anti-inflammatory agents with a significant decrease in vascular permeability. (no Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

72. DELTA(1)-TESTOLOLACTONE: CLINICAL TRIALS.

Segaloff A
Div. Endocrine Res., Ochsner Medical Institutions, New Orleans, LA, 70121
Cancer Res; 42(8,Suppl):3387s-3388s 1982

Delta(1)-Testololactone (testolactone, 1-dehydrotestololactone, Teslac, 17alpha-oxa-D-homo-1,4-androstadiene-3,17-dione) was tested in advanced human breast cancer despite its lack of activity against animal tumor systems. This was done because D-ring lactones were thought to be obligatory intermediates of steroid metabolism. The clinical trials showed substantial activity against breast cancer with the optimal po dose of 1 g/day. (Author abstract) (12 Refs)

73. HIGH-DOSE MEDROXYPROGESTERONE ACETATE FOR THE TREATMENT OF ADVANCED OVARIAN CARCINOMA.

Trope C, Johnsson JE, Sigurdsson K, Simonesen E
Gynecologic Section, Dept. Oncology, Univ. Hosp., S-221 85 Lund, Sweden
Cancer Treat Rep; 66(6):1441-1443 1982

Effects of high-dose medroxyprogesterone acetate (MPA) were studied in 25 patients (43-81 yr old, median 61 yr) with recurrent, advanced (7 patients Stage III, 18 Stage IV) and chemotherapy-resistant ovarian carcinoma, with measurable or evaluable lesions. MPA was given im 500 mg/day for 3 wk, followed by 500 mg once a wk for at least 2 mo. Patients with an objective response or stable disease continued treatment with 500 mg every wk until disease progression. One patient achieved partial response (duration, 3+ mo; survival 4+ mo); 9 had stable disease (median duration, 5.5+ mo; median survival, 6.5 mo); and 15 had progressive disease (median survival, 3 mo). The objective response occurred in a 73-yr-old woman with undifferentiated carcinoma Stage IV. The patient had a greater than 50% reduction of central pelvic mass and inguinal nodes. Nine (36%) of the 25 patients increased their Karnofsky index by an av of 20 points. During therapy, no changes in blood counts or serum levels of creatinine, bilirubin, alkaline phosphatase, and fasting blood sugar were observed. More severe complications such as deep vein thrombosis were observed in two patients, but both had large pelvic tumors and had possibly developed thrombosis. The overall response rate was 4%. Since most of the epithelial ovarian carcinoma cell types were included in the study, results indicated that objective responses may be obtained only in a minority of patients with ovarian carcinoma resistant to cytostatic drugs. (5 Refs)

74. TRIAL OF TAMOXIFEN AT A DOSE OF 40 MG DAILY AFTER DISEASE PROGRESSION DURING TAMOXIFEN THERAPY AT A DOSE OF 20 MG DAILY.

Stewart JF, Minton MJ, Rubens RD
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Cancer Treat Rep; 66(6):1445-1446 1982

A prospective nonrandomized trial was conducted in 36 consecutive patients (av age 64.9 yr) to assess the response of advanced breast cancer to 20 mg tamoxifen (TO) bid after disease progression during therapy with 10 mg bid. The patients studied had histologically confirmed, locally advanced inoperable or metastatic breast cancer that was progressing during treatment with 10 mg TO bid with or without 5 mg prednisone (PR) bid. Characteristics of the 30 evaluable patients are presented. No objective responses to the higher dose of TO were observed. Seven patients had stable disease for 2-15 mo, two who had responded to previous endocrine therapy (TO, PR), and five who had had no prior response. These patients comprised two with estrogen receptor (ER)-positive (greater than or equal to 5 femtomole; fmol/mg of cytosol protein) tumors, one with ER-negative (less than 5 fmol/mg of cytosol protein) tumor, and four with unknown ER tumor status. The other 23 patients all had progressive disease. Median time to treatment failure was 2 mo (range 1-15 mo), and median survival from study entry was 11 mo (range 2-17 mo). Results indicated that escalation of TO dosage to 20 mg bid after disease progression during therapy with 10 mg bid does not lead to further response and that alternative therapy, either endocrine or cytotoxic, should be given. (5 Refs)

75. BRENNER'S TUMOR OF THE OVARY, SYNOPSIS OF CLINICAL DATA AND HISTOLOGICAL FINDINGS.

Kostal M, Andrys J, Kopecny J
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Cesk Gynekol; 47(4):279-283 1982

Brenner's tumors of the ovary were diagnosed in 14 patients (49-78 yr old) during the period 1966-1981. There was only one nullipara among the 14 patients, the other 13 had had 1-7 childbirths. Twelve of the 14 patients were in menopause for 0.5-28 yr. Twelve of the 14 patients had symptoms, including mostly obstipation, metrorrhagia, and spotting. Brenner's tumor coinciding with adenocarcinoma of the uterine body was found in one patient, bilateral Brenner's tumor in another. Brenner's tumors were solid cystic in 4/14 patients, solid in 10. Treatment consisted of surgery in all cases: abdominal hysterectomy was performed in 5/14 patients, vaginal hysterectomy in 2/14, supracervical amputation in 1/14 and adnexectomy in 6/14. Hysterectomy and amputation were complemented by adnexectomy in all eight patients. No postoperative complications were observed. The possible risk of malignant transformation of Brenner's tumor and long-term estrogen stimulation of the target tissue by the tumor are emphasized. (11 Refs) (In CZE)

76. EFFECT OF HIGH-DOSE OESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMOURS IN THE RAT.

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J Endocrinol; 93(1):11-16 1982

The effect of chronic administration of a high dose of estradiol benzoate (OB) on growth and prolactin receptor content of the N-nitrosomethylurea (NMU)-induced rat mammary tumor was investigated. Daily im administration of 50 ug OB for 8 days to tumor-bearing rats induced marked reduction in tumor size which was already significant after only three injections. Simultaneous daily administration of 1 mg perphenazine to stimulate endogenous prolactin release counteracted the inhibitory effect on tumor growth of OB but only partially since the tumors grew significantly more when perphenazine was injected alone. No treatment significantly affected prolactin receptor content in the tumors. We concluded that administration of pharmacological doses of OB has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of the peripheral action of prolactin. (Author abstract) (22 Refs)

77. EFFECTS OF AROMATASE INHIBITOR 4-HYDROXYANDROSTENEDIONE AND OTHER COMPOUNDS IN THE 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED BREAST CARCINOMA MODEL.

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Cancer Res; 42(8,Suppl):3360s-3364s 1982

Aromatase inhibitor, 4-hydroxyandrostene-3,17-dione (4-OHA), is a highly effective treatment in rats with 7,12-dimethylbenz(a)anthracene-induced hormone-dependent mammary tumors. Over 90% of tumors regress to less than one-half of their original size, and a high proportion regress completely. Treatment of rats with other inhibitors, 4-acetoxyandrostene-3,17-dione and 1,4,6-androstatriene-3,17-dione produce similar results. In comparison with other aromatase inhibitors, the compounds reduced ovarian estrogen secretion in the rat to the same extent as aminoglutethimide, whereas Teslac was without effect. The latter two compounds caused little and no regression of DMBA-induced mammary tumors, respectively. Our recent studies with 4-OHA, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatriene-3,17-dione indicate that they interact with aromatase by a two-component mechanism, a rapid competitive inhibition, and a slower enzyme inactivation. Treatment of rats with 4-OHA also caused greater than 80% loss of ovarian aromatase activity in vivo and a reduction in ovarian estrogen secretion, which are maintained for at least 48 hr after injection. Although 4-OHA is cleared rapidly in vivo, the above results suggest that the compound has a sustained effect. Thus, when 7,12-dimethylbenz(a)anthracene-induced tumor-bearing rats were treated with 4-OHA injections on alternate wk, tumor regression continued to occur during wk without treatment. The overall regression was similar to that with continuous treatment. 4-OHA is also effective and similar to ovariectomy in rats with hormone-dependent metastatic mammary tumors produced by nitrosomethylurea. Our results indicate that mammary tumor regression induced by 4-OHA is mainly the result of the inhibition of aromatization, although other activities of the compound may also contribute. (Author abstract) (23 Refs)

78. TREATMENT OF ADVANCED BREAST CANCER WITH AMINOGLUTETHIMIDE: A 14-YEAR EXPERIENCE.

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Cancer Res; 42(8,Suppl):3389s-3396s 1982

Aminoglutethimide, derived from a nonbarbiturate soporific and originally introduced as an anticonvulsant drug, was subsequently discovered to inhibit steroid biosynthesis by interfering with the enzymatic conversion of cholesterol to delta(5)-pregnenolone. It has been found to interfere with the aromatization of androstenedione. This study is designed to exploit the hormone-manipulative property of aminoglutethimide in the treatment of advanced breast cancer. From July 1967 of July 1981, 91 women possessing histologically diagnosed symptomatic measurable advancing metastatic breast cancer refractory to current conventional therapy, including hormonal, were consecutively entered into the treatment study using aminoglutethimide with low-dose dexamethasone as a 'medical adrenalectomizer' in poor-risk patients. No patients possessed solely skin and soft tissue metastases. Preterminal patients were included in this study. Biochemical indices of adrenocortical and gonadal function were obtained pretreatment and periodically thereafter. Response criteria were established by the Eastern Cooperative Oncology Group. Patients with subjective and stabilization responses were considered nonresponders. Median survival time of responding patients was 22 mo, compared with 2 mo for nonresponding patients. Twenty-five of 73 patients with visceral dominant lesions responded. Initial patient performance status and dominant metastatic lesion were unrelated to response, but disease-free interval and site of relapse were related to drug toxicity. Treatment with aminoglutethimide provides effective palliation in poor-risk patients with advanced breast cancer with a response rate and survival time equal to those reported in better-risk patients following surgical adrenalectomy. (27 Refs)

79. ADEQUACY OF ESTROGEN SUPPRESSION WITH AMINOGLUTETHIMIDE AND HYDROCORTISONE AS TREATMENT OF HUMAN BREAST CANCER: CORRELATION OF HORMONAL DATA WITH CLINICAL RESPONSES.

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Cancer Res; 42(8,Suppl):3397s-3401s 1982

Human breast neoplasms can be divided into hormone-dependent and hormone-independent subtypes. Estrogen is the major hormonal stimulus for growth of the dependent tumors. Failure to respond to estrogen suppression therapy could reflect either an incomplete lowering of estrogens or the hormonal independence of the tumor. We compared the levels of several estrogens and other hormones in women experiencing objective responses and disease progression during therapy with the aromatase-steroidogenesis inhibitor, aminoglutethimide, and replacement hydrocortisone. Pretreatment hormonal profiles of the estrogens, androgens, ketosteroids, thyroxine, polypeptide hormones, and carcinoembryonic antigen did not differ significantly among response groups. During treatment, the levels of all estrogens were suppressed to a similar degree in the progression group and in the responders. Data suggested that lack of estrogen suppression did not explain the response to treatment in the patients receiving aminoglutethimide-hydrocortisone. This finding differs from our results in a similarly analyzed control group of patients treated with surgical adrenalectomy. Levels of the weak androgens, dehydroepiandrosterone sulfate and androstenedione, were found to be higher in the progression group compared to the responders. This observation could not be explained by differences in duration of treatment between groups. Analysis at 1 to 12 wk, 13 to 24 wk, and 25 to 36 wk after initiating treatment indicated higher androgen levels at each time point in the progression group. While the finding of higher androgen levels in the responder group remains unexplained, this study indicates that incomplete estrogen suppression is not responsible for lack of tumor response in patients with progressive disease during aminoglutethimide-hydrocortisone therapy. (21 Refs)

80. AMINOGLUTETHIMIDE IN THE TREATMENT OF METASTATIC BREAST CANCER.

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Cancer Res; 42(8,Suppl):3402s-3404s 1982

Aminoglutethimide in combination with dexamethasone has been used in 44 patients with metastatic breast cancer who had prior response to hormonal manipulation and/or positive estrogen receptors. Objective tumor response - complete response plus partial response - has been achieved in 19 of 44 patients. Responses were seen in soft tissue, bone, and pleura. Eleven of 44 patients had stable disease, and 14 patients had progressive disease. The median duration of response was 8 mo. Side effects were moderate, including lethargy, rash, fever, and Cushingoid facies. This treatment is well tolerated and is an effective hormone manipulation in postmenopausal patients with metastatic breast carcinoma. (Author abstract) (9 Refs)

81. ADJUVANT AMINOGLUTETHIMIDE THERAPY FOR POSTMENOPAUSAL PATIENTS WITH PRIMARY BREAST CANCER: PROGRESS REPORT.

Coombes RC, Chilvers C, Dowsett M, Gazet JC, Ford HT, Bettelheim R, Gordon C, Smith IE, Zava D, Powles TJ, McKinna A, White H, Henk M, Griffiths M, Bradbeer J, Neeley J, Bull JC, Topham C, Hunter-Craig I, Hale JE, Folkes A, Taylor R, Miller S, Southam JA, Tostam A, Booth RA, Gazet JC, Nash A
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey, SM2 5PX, England
Cancer Res; 42(8,Suppl):3415s-3419s 1982

A group of 122 postmenopausal patients with histologically proven node-positive primary breast cancer have been randomized to receive aminoglutethimide-hydrocortisone or placebo aminoglutethimide-placebo hydrocortisone for 2 yr. Median follow-up is 17 mo. In general treatment was well tolerated, but 15 patients required a reduction in the dose of aminoglutethimide, and of these four patients were unable to continue therapy due to side effects. Primary staging, incidence of extensive node involvement, and estrogen receptor were similar in the treatment and control arms. Dehydroepiandrosterone sulfate (DHA-S) and estrone were measured in a subgroup of patients, and significant suppression of DHA-S levels throughout the duration of the treatment period was seen in patients receiving the active drug. No significant suppression of either DHA-S or estrone levels was seen in the controls. Patients were monitored for metastases by serial liver function tests, carcinoembryonic antigen, and chest x-rays, and of 26 relapsing patients only 3 patients were not detected by this screen. We conclude that adjuvant aminoglutethimide is moderately well tolerated. It is capable of suppressing DHA-S throughout 2 yr of treatment. A further 280 patients will be entered into the study to assess the survival benefit for those taking aminoglutethimide-hydrocortisone. (Author abstract) (8 Refs)

82. ANTIESTROGEN TREATMENT OF BREAST CANCER: AN OVERVIEW.

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Cancer Res; 42(8,Suppl):3424s-2429s 1982

Tamoxifen has emerged as a highly effective, nontoxic endocrine therapy for women with Stage IV and II estrogen receptor-positive breast cancer. Tamoxifen appears to act by blocking endogenous estrogen action at the target tissue level rather than by suppression of circulating estrogen levels. In a series of 113 consecutive, selected patients with Stage IV breast cancer, tamoxifen induced objective remissions in 50%. Recent randomized studies comparing pharmacological doses of estrogen vs tamoxifen in postmenopausal women with Stage IV breast cancer have shown comparable results with these two modalities. Antiestrogen therapy has been shown to be effective in some patients after prior endocrine additive therapy and, in particular, after ablative procedures, such as ovariectomy, adrenalectomy, and hypophysectomy. It has been shown that circulating estrogens are not completely eliminated following ablation of these endocrine glands, which may account for the effectiveness of antiestrogen in this setting. Other endocrine therapies have been shown to be effective after prior treatment with antiestrogen. Recent studies have shown that aminoglutethimide plus hydrocortisone may also induce remissions in some patients after prior treatment with tamoxifen. This latter finding is of particular interest since aminoglutethimide is thought to work by blocking estrogen production, and the finding suggests that tamoxifen does not completely block all endogenous estrogen activity. Fluoxymesterone has been shown to induce remissions after tamoxifen or after tamoxifen plus hypophysectomy, and there was no correlation between the response to antiestrogen and subsequent response to androgen. Because of its effectiveness and minimal side effects, tamoxifen is considered to be an initial endocrine therapy of choice in women with breast cancer. However, it has its limitations, as demonstrated by the results of secondary endocrine therapies such as hypophysectomy, medical adrenalectomy, and androgen therapy. (28 Refs)

83. TAMOXIFEN VERSUS AMINOGLUTETHIMIDE VERSUS COMBINED TAMOXIFEN AND AMINOGLUTETHIMIDE IN THE TREATMENT OF ADVANCED BREAST CARCINOMA.

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Cancer Res; 42(8,Suppl):3430s-3433s 1982

In a control randomized cross-over trial, 117 patients with advanced breast cancer were treated initially either with tamoxifen (10 mg po twice daily) or aminoglutethimide (250 mg po 4x daily) with hydrocortisone (20 mg twice daily). Patients failing to respond or relapsing were switched to the alternative treatment. Eighteen (30%) of the 60 patients initially treated with tamoxifen achieved an objective response, and 11 (18%) achieved stable disease. Seventeen (30%) of the 57 patients treated initially with aminoglutethimide achieved an objective response, and 13 (23%) achieved stable disease. Aminoglutethimide achieved a 35% objective response and a further 26% subjective bone pain relief in patients with bone metastases (overall, 61%) compared with a 17% objective response and a further 17% objective bone pain relief with tamoxifen (total, 34%). None of six premenopausal patients responded to aminoglutethimide compared with two of four responding to tamoxifen. The median response duration to aminoglutethimide was 16 mo compared with 20 mo for tamoxifen. Side effects for aminoglutethimide (including lethargy, rash, and depression) were more common than for tamoxifen, and 7% of aminoglutethimide-treated patients had to discontinue treatment because of these compared with 0% on tamoxifen. In cross-over studies, 6 of 12 tamoxifen responders who relapsed achieved a second response to aminoglutethimide (50%), as did 6 of 29 patients who initially failed to respond to tamoxifen (21%). In contrast, none of 11 patients relapsing after response to aminoglutethimide achieved a second response to tamoxifen; only 1 of 18 nonresponders to aminoglutethimide subsequently responded to tamoxifen (6%). In a subsequent study in which 62 patients were treated with combined tamoxifen and aminoglutethimide, the overall response rate of 37% was not significantly better than that for either agent used alone. (Author abstract) (12 Refs)

84. RANDOMIZED TRIAL OF AMINOGLUTETHIMIDE VERSUS TAMOXIFEN IN METASTATIC BREAST CANCER.

Lipton A, Harvey HA, Santen RJ, Boucher A, White D, Bernath A, Dixon R, Richards G, Shafik A
Central Pennsylvania Oncology Group, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(8,Suppl):3434s-3436s 1982

We compared antiestrogen therapy (tamoxifen) with an estrogen suppression regimen (aminoglutethimide-hydrocortisone) in postmenopausal women with metastatic breast carcinoma. Fifteen of 39 patients (38%) who received tamoxifen experienced an objective tumor regression (3 complete, 12 partial remissions), whereas 13 of 36 women (36%) receiving aminoglutethimide responded (1 complete remission, 12 partial remissions). The median duration of response was similar. The site of tumor involvement appears to be important in choosing between these hormonal treatments. Aminoglutethimide appears to offer a greater chance of response in patients with bone involvement. (Author abstract) (18 Refs)

85. PHASE II STUDY OF AMINOGLUTETHIMIDE AND MEDROXYPROGESTERONE ACETATE IN THE TREATMENT OF PATIENTS WITH ADVANCED BREAST CANCER.

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Cancer Res; 42(8,Suppl):3442s-3444s 1982

Forty-five women with far-advanced metastatic breast cancer were treated with a combination of aminoglutethimide (AG), 1,000 mg po daily, and medroxyprogesterone acetate (MPA), 1,500 mg po daily. Of 41 patients evaluable for treatment response, there were 2 complete responses, 5 partial remissions, 26 patients with minor tumor responses or no change, and 8 nonresponders. Major side effects included those known for AG and MPA, ie, impairment of mental functions, depressive syndromes, fatigue, ataxia, skin rash, changes in body wt, and transient increase of gamma-glutamyltransferase. Most side effects disappeared spontaneously after 4 to 6 wk of treatment. Plasma hormone measurements in 28 patients revealed no impairment of adrenocorticotropic hormone and cortisol levels. In conclusion, in the AG combination, it is feasible and safe to replace cortisol by MPA. Treatment results warrant further investigation of AG-MPA in patients with breast cancer of a more favorable prognosis. (Author abstract) (5 Refs)

86. CROSS-OVER COMPARISON OF TAMOXIFEN AND AMINOGLUTETHIMIDE IN ADVANCED BREAST CANCER.

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Cancer Res; 42(8,Suppl):3451s-3453s 1982

Thirty-four postmenopausal patients with advanced breast cancer had an overall objective response rate of 47% when treated with aminoglutethimide and hydrocortisone initially and a response rate of 24% when crossed over to therapy with tamoxifen after progression on aminoglutethimide. A similar group of 32 patiens experienced a response rate of 28% when treated with tamoxifen first and a 19% objective response rate on subsequent therapy with aminoglutethimide. Patients who failed to respond to the first therapy seldom responded on cross-over to the alternate therapy. Toxicities were acceptable with both forms of therapy. Tamoxifen and aminoglutethimide used sequentially are effective forms of palliative hormonal therapy in metastatic breast cancer. (Author abstract) (8 Refs)

87. CLINICAL TRIAL OF MULTIPLE ENDOCRINE THERAPY FOR METASTATIC AND LOCALLY ADVANCED BREAST CANCER WITH TAMOXIFEN-AMINOGLUTETHIMIDE-DANAZOL COMPARED TO TAMOXIFEN USED ALONE.

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Cancer Res; 42(8,Suppl):3458s-3460s 1982

Multiple-endocrine therapy with combinations of various types of treatment has not been evaluated properly in spite of the success of individual types of hormone treatment. This paper reports the early results of a randomized controlled clinical trial comparing tamoxifen (10 mg 2x/day)-aminoglutethimide (250 mg 3x/day)-danazol (100 mg 3x/day)-hydrocortisone (20 mg 2x/day) (TAD) with tamoxifen (10 mg 2x/day). Analysis of the first 107 assessable patients indicates objective response (criteria of the International Union Against Cancer) in 33% of patients receiving tamoxifen vs 50% of patients receiving TAD. Duration of response to TAD is identical to duration of response to tamoxifen alone. TAD is well tolerated, and toxicity, although greater than for tamoxifen, is acceptable. (Author abstract) (20 Refs)

88. PROGRESS REPORT ON TWO CLINICAL TRIALS IN WOMEN WITH ADVANCED BREAST CANCER. TRIAL I: TAMOXIFEN VERSUS TAMOXIFEN PLUS AMINOGLUTETHIMIDE; TRIAL II: AMINOGLUTETHIMIDE IN PATIENTS WITH PRIOR TAMOXIFEN EXPOSURE.

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Cancer Res; 42(8,Suppl):3461s-3467s 1982

A progress report is presented on two on-going clinical trials in women with advanced breast cancer. In Trial I to date, 56 patients have been randomized to tamoxifen (TAM) alone or TAM plus aminoglutethimide (AG) (plus hydrocortisone). Patients failing TAM can then receive AG. The two groups are reasonably well balanced with respect to prior hormonal therapy exposure (TAM, 19%; TAM plus AG, 17%), age, disease-free interval, performance score, and estrogen receptor status. The TAM plus AG group has a higher incidence of visceral dominant disease (41 vs 26%) and prior chemotherapy exposure (41 vs 33%). Responses have been observed in 7 of 27 (26%) patients on TAM and 11 of 28 (39%) on TAM plus AG. Median times to treatment failure (defined as disease progression, unacceptable toxicity, or patient refusal) are 211 and 123 days, respectively (log-rank on time to treatment failure, $p = 0.87$). Toxicity is greater for TAM plus AG with a higher incidence of skin rash, lethargy, and dizziness. Thrombotic events were seen in one patient on TAM and two patients on TAM plus AG. One patient on TAM plus AG developed leukopenia and sepsis. The data are too preliminary for one to draw firm conclusions regarding relative efficacy. In Trial II to date, 35 patients with prior tamoxifen exposure have received AG. The mean number of prior systemic therapies is 3.2 (range, 1 to 7). The response rate is 20% and similar with (21%) or without (19%) prior chemotherapy exposure. The median time to treatment failure is 92 days. One patient developed leukopenia and sepsis. Additional patient accrual is necessary to allow characterization of potential efficacy within prognostically important subsets. (Author abstract) (10 Refs)

89. LACK OF CORRELATION BETWEEN TRANSFORMED CHARACTERISTICS IN CULTURE AND TUMORIGENICITY OF MOUSE MAMMARY TUMOUR CELLS.

Yates J, King RJ

Cell Biology Div., Glaxo Group Res., Greenford, Middlesex, England

Eur J Cancer Clin Oncol; 18(4):399-403 1982

Androgen responsive and unresponsive Shionogi 115 mouse mammary carcinoma cells have been examined for anchorage-independent growth and tumorigenicity in nude mice. The two cell types exhibit transformed and normal growth characteristics respectively, but both give rise to tumors in nude mice. No correlation between tumorigenicity and transformed characteristics including anchorage-independent growth could be demonstrated. (Author abstract) (11 Refs)

90. THE RELATION BETWEEN THE STATUS OF ADAPTIVE SYSTEM AND THE NUMBER OF POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH GASTROINTESTINAL CANCER: THE EFFECT OF PHENAZEPAM.

Ostroumova MN, Simonov NN, Kovalev VK, Bernstein MI
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J Surg Oncol; 20(3):192-196 1982

The decrease in 11-hydroxycorticosteroids concentration caused by 0.5 mg of dexamethasone administered at 11 pm was studied in 91 primary patients suffering from gastrointestinal cancer. In dexamethasone-resistant patients postoperative complications developed in 65% of colon cancer patients and in 42% of stomach cancer patients. In dexamethasone-sensitive patients the complications were observed in 24% and 12% of patients, correspondingly. The elevation of hypothalamic threshold of sensitivity to the inhibiting effect of glucocorticoids, revealed by the dexamethasone suppression test, was considered to be a result of a combined action of age, the tumor itself, and pronounced emotional stress during the preparation for operation. The derivative of benzodiazepin - phenazepam - when administered before the operation in colon cancer patients improved the results of the dexamethasone suppression test and decreased the number of postoperative complications. (Author abstract) (24 Refs)

91. EFFECT OF AN AROMATASE INHIBITOR, 1,4,6-ANDROSTATRIENE-3,17-DIONE, ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT AND ITS MECHANISM OF ACTION IN VIVO.

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Biochem Pharmacol; 31(11):2017-2023 1982

In this study, 1,4,6-androstatriene-3,17-dione (ATD) was demonstrated to cause time-dependent loss of aromatase activity in rat ovarian microsomes in vitro. In vivo, an injection of ATD caused inhibition of ovarian aromatase and reduced estrogen secretion in pregnant mare's serum gonadotropin-primed rats for at least 24 hr after injection. In rats with 7,12-dimethylbenz[a]anthracene-induced, hormone-dependent, mammary tumors, marked regression occurred with ATD treatment. Although estrogen secretion was not reduced below the diestrus level of controls, the rats remained anestrus, indicating that the proestrus surge of estrogen was prevented. LH, FSH and prolactin levels were also basal and LH and FSH did not rise after ovariectomy. ATD had no detectable hormonal activity in bioassay. Consistent with this, the compound did not interact appreciably with either androgen or estrogen receptors, was not uterotrophic, and did not interfere with mammary tumor regression in ovariectomized rats. Thus, the major activities of the compound which cause mammary regression in the rat appear to be inhibition of estrogen synthesis, via aromatase and gonadotropin suppression. (Author abstract) (24 Refs)

92. SURVIVAL AMONG WOMEN WITH ENDOMETRIAL CANCER: A COMPARISON OF ESTROGEN USERS AND NONUSERS.

Chu J, Schweid AI, Weiss NS
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Am J Obstet Gynecol; 143(5):569-573 1982

In order to determine the role of postmenopausal estrogen use in survival of patients with endometrial cancer, we identified, through a population-based tumor registry serving the area, all white women in King County, Washington, aged 50 to 74, who developed endometrial cancer between January, 1975, and April, 1976 (N = 363). Estrogen use prior to diagnosis and survival status were ascertained through personal interview, medical records of private physicians, and registry follow-up data. The 4-yr relative survival ratio in estrogen users was 1.05 compared to 0.898 in nonusers. Overall, after adjustment for age, the survival in estrogen users was significantly better than in nonusers (Chi2 = 30.5; p much less than 0.0001). While estrogen use may predispose to an increased incidence of endometrial cancer, it appears that such use does not lead to increased mortality from this condition. (Author abstract) (25 Refs)

93. ETHYLNITROSOUREA-INDUCED THYROID TUMORS IN RATS.

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All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(3):68-70 1982

Effect of ethylnitrosourea (ENU: 30 mg/kg, ip) on thyroid carcinogenesis was studied in random-bred albino rats subjected to transplacental exposure to sex hormones. Estrogens and androgen were administered to pregnant females on Days 19, 20, and 21 of gestation, and the ENU was administered to the offspring when they were 16-20 days old or 4-6 mo old. The incidence of spontaneous thyroid tumors (solid and follicular adenomas) was 3%. Transplacental administration of the sex hormones, without administration of the ENU, induced thyroid tumors in 13-15% of the males and in 7-8% of the females; almost all of the rats developed solitary adenomas. ENU administration, without prior administration of sex hormones, induced thyroid tumors in 57% of the immature males and 58% of the immature females. Administration of the sex hormones prior to administration of the ENU did not affect the incidence of ENU-induced thyroid tumors in the immature males (40-50%) but reduced the incidence in the immature females (24-28%). ENU administered alone or in combination with sex hormones did not affect the incidence of thyroid tumors in the mature rats. (8 Refs) (In RUS)

94. GROWTH RESPONSES OF RAT STOMACH CANCER CELLS TO GASTRO-ENTERO-PANCREATIC HORMONES.

Kobori O, Vuillot MT, Martin F
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Int J Cancer; 30(1):65-67 1982

Various hormones and peptides were added to rat stomach cancer cells growing in vitro in a serum-free medium and the cell number was determined by a spectro-photometric method. Five gastro-entero-pancreatic hormones or related peptides (tetragastrin, glucagon, secretin, cholecystokinin-pancreozymin and cerulein) significantly increased the number of stomach cancer cells from 150% to 310% of the number of control cells cultivated in a serum-free, hormone-free medium. On the other hand, insulin and vasoactive intestinal peptide, and other hormones (thyroxin, epinephrine, hydrocortisone, beta-estradiol, progesterone, testosterone), peptone broth and bovine serum albumin had no significant growth effect. All the active substances belong to the two major families of gastro-entero-pancreatic polypeptide hormones, suggesting the existence of hormone receptors at the surface of stomach cancer cells. (Author abstract) (10 Refs)

95. THE SYNTHESIS OF 3H LABELLED STEROID-NITROGEN MUSTARD DERIVATIVES AND STUDIES ON THEIR ACTION IN RAT AND HUMAN PROSTATE.

Symes EK, Milroy EJ
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J Steroid Biochem; 17(1):23-30 1982

The synthesis of 3H-labeled 5alpha-dihydrotestosterone 17betaN-bis-(2-chlorethyl)carbamate (3H-DHT-NM) is reported and studies of its action in rat and human prostatic tissue was compared with that of 3H-estramustine-nitrogen mustard (3H-E2-NM). The relative binding affinities of these compounds compared with that of 5alpha-dihydrotestosterone (DHT) were in the order of 100:0.1:0.005 (DHT:DHT-NM:E2-NM). Following ip injection of 25 uCi of 3H-E2-NM or 3H-DHT-NM, to 24 hr castrate rats, the relative tissue distribution of the compounds differed only slightly, while the percent of the total dose recovered was 5-10x greater after injection of 3H-E2-NM than after injection of 3H-DHT-NM. Uptake of steroids and E2 in human benign prostatic tissues was similar but significantly greater than the uptake of DHT-NM. The half lives in vivo were in the order of E2-NM greater than DHT-NM greater than or equal to estradiol-17beta greater than DHT greater than or equal to testosterone, while measurements in vitro appeared to reverse the trend seen in vivo. Cleavage rates of DHT-NM and E2-NM were similar but considerably greater during incubation at 10(-5) than at 10(-8) M. In five specimens of human carcinomatous tissue, cleavage rates were low. Cleavage rates in various rat tissues were similar, but very low in the brain. Use of DHT-NM does not appear to offer any advantage with respect to selective tissue retention, metabolic activation, or nuclear translocation, over use of E2-NM. (23 Refs)

96. EFFECTS OF STEROID SEX HORMONES AND ADRIAMYCIN ON HUMAN BLADDER CANCER CELLS IN CULTURE.

Yoshimoto J, Matsumura Y, Tanahashi T, Ohmori H, Tokiwa T, Sato J
Dept. Urology, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Med Okayama; 36(1):61-66 1982

The effects of steroid sex hormones on the established cell lines derived from human urinary bladder cancer, T24 and from human transitional cell cancer of the urinary tract, 253J, were examined using the colony formation method. Of the seven kinds of steroid hormones tested, estradiol-17beta was intensively cytotoxic for both cells. The cytotoxic effect was depended on the dose and time of treatment. The combined effect of Adriamycin and estradiol-17beta on T24 cells could be recognized at low concentrations of Adriamycin (less than or equal to 10(-3) ug/ml) after exposure for 24 hr. (Author abstract) (12 Refs)

97. VISUALIZATION OF SKELETAL MUSCLE INVOLVEMENT OF MYCOSIS FUNGOIDES ON 67GA SCINTIGRAPHY.

Shigeno C, Morita R, Fukunaga M, Tsuchiya K, Hino M, Harioka T, Torizuka K
Dept. Nuclear Medicine, Kytoto Univ. Sch. Medicine, 54 Shogoin-kawara-machi, Kyoto 606, Japan
Eur J Nucl Med; 7(7):333-335 1982

An uncommon involvement of the skeletal muscle by mycosis fungoides detected by 67Ga-citrate scintigraphy in a 84-yr-old female is described. The patient developed generalized erythema 17 yr prior to the admission. The patient was successfully treated with corticosteroids and regional radiotherapy. For the following 15 yr the patient's condition had remained good until 2 mo prior to the admission. Diagnosis of mycosis fungoides was made by skin biopsy. The patient was treated with systemic chemotherapy and with regional radiotherapy. The patient's condition progressively deteriorated. The patient died of bronchopneumonia approx 6 wk after 67Ga scanning. Autopsy section from the left leg showed diffuse infiltration of malignant lymphomatous cells in all soft tissue components from the skin to the underlying calf muscle. (11 Refs)

98. FLUTAMIDE IN ADVANCED CANCER OF THE PROSTATE (MEETING ABSTRACT).

Kassem NY, Neri RO
Department of Clinical Research, Schering Corporation, Bloomfield, NJ
Eighty-third Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, March 17-20, 1982, Lake Buena Vista, Florida. American Society for Clinical Pharmacology and Therapeutics 87 pp., 1982.

Thirteen investigators studied the effect of 250 mg flutamide tid on stage D prostatic cancer in 243 patients. Seventy-six patients were castrates and 167 noncastrates. Sixty-nine castrates and 59 noncastrates had been previously treated with estrogens, which had been discontinued for refractoriness in 45%, no response in 14%, cardiovascular complications in 15%, and other reasons in 26%. Parameters of response to flutamide included improvement in pain, prostatic enlargement and induration, metastases, body weight, and acid phosphatase. The results indicated an overall positive response to flutamide in 39% of the castrates previously treated with estrogens, 59% of the noncastrates previously treated with estrogens, and 75% of the castrates and 87% of the noncastrates who were not previously treated with estrogens. The most common adverse effects were the gynecomastia and breast tenderness that occurred in 34% of the patients and occasional nausea and vomiting. Thromboembolic/cardiovascular complications occurred in seven patients: four had been treated with estrogens and one had thrombophlebitis prior to, and one shortly after, the initiation of flutamide therapy; the latter subsequently resolved while on therapy. One patient, a diabetic, developed pulmonary edema because of water overload. We conclude that flutamide is an efficacious and safe drug in the treatment of cancer of the prostate. (no Refs)

GENERAL REVIEWS ON STEROID HORMONES

99. EDITORIAL: DRUG THERAPY OF PROSTATIC CANCER.

Benson RC, Utz DC, Murphy GP
Mayo Clinic, Rochester, MN
Urology; 19(6):621-622 1982

Treatment of prostatic cancer (PC) with estramustine phosphate (EP) is reviewed. In PC patients who have had prior orchiectomy, response rates to EP vary from 26-53%. In non-castrated but refractory PC patients, response rates of 41-63% have been observed. Estrogenic effects of EP are described. Side effects of EP include gastrointestinal discomfort and nausea. EP and estrogen therapy of PC are compared with regard to efficacy and side effects. (8 Refs)

100. BIOCHEMICAL MARKERS FOR CANCER.

Chu TM
Dept. Diagnostic Immunology Res. and Biochemistry, Roswell Park Memorial Inst., Buffalo, NY
Clin Biochem Anal; 11:375pp. 1982

Selected topics on biochemical markers, which have been utilized in clinical oncology, are presented and a possible approach to the study of the basic mechanism of the marker at the molecular level is described. Topics related to biochemical markers are discussed under the following headings: immunological approach to the biochemical markers for cancer, alpha fetoprotein, carcinoembryonic antigen as a tumor marker, enzymes as tumor markers, developmental alkaline phosphatases as biochemical tumor markers, prostatic acid phosphatase in human prostate cancer, biochemical markers for the differential diagnosis of leukemias, steroid-receptor interactions in normal and neoplastic mammary tissues, alteration and clinical significance of alteration of isoferritins in human malignancy, polyamines as biochemical markers of tumor growth parameters, ectopic hormone production by tumors, immunoglobulins as cancer markers in humans, multiple markers in the management of cancer patients, protein markers for androgenic activity in rat ventral prostate. (1283 Refs)

101. SIDE EFFECTS OF DRUGS. ANNUAL 6. A WORLDWIDE YEARLY SURVEY OF NEW DATA AND TRENDS.

Dukes MN, Elis J
Netherlands Commitee for the Evaluation of Medicines, Ministry of Health, Koopmanstraat 1, 2288 BC Rijswijk, The Netherlands
Side Eff Drugs Annu 6: 478 pp., 1982.

Current information relating to adverse drug reactions and interactions from the clinical point of view is presented. Drugs are classified according to primary field of application or for the properties for which they are most generally recognized. In borderline cases some supplementary discussion has been included relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component. Agents covered include CNS stimulants and anorectic agents; antidepressants; lithium; social drugs; hypnotics; sedatives; anticonvulsants; opioid analgesics; narcotic antagonists; antipyretic analgesics; anti-inflammatory analgesics and drugs used in rheumatoid arthritis and gout; general anesthetics; therapeutic gases; local anesthetics; muscle relaxants; drugs affecting autonomic functions or the extrapyramidal system; drugs used on the skin; antihistamines; drugs used in bronchial asthma and cough; cardiac glycosides; drugs used in dysrhythmias; anti-anginal and beta-adrenoreceptor blocking drugs; drugs acting on the peripheral circulation; hypotensive drugs; diuretic drugs; metals; metal antagonists; antiseptic drugs and disinfectants; penicillins; cephalosporins; tetracyclines; other antibiotic drugs; antifungal drugs; antiprotozoal drugs; sulfonamides; miscellaneous antibacterial and antiviral drugs; drugs used in tuberculosis and leprosy; anthelminthic drugs; enzymes; enzyme inhibitors; immunologic preparations; blood and blood products; iv infusions (soln and emulsions); drugs affecting blood clotting, fibrinolysis, and hemostasis; gastrointestinal drugs; drugs used in the management of gallstones; vitamins; corticosteroids; corticotrophins; sex hormones and related compounds including oral contraceptives; thyroid and antithyroid drugs; insulin; glucagon; oral hypoglycemic drugs; miscellaneous hormones and prostaglandins; drugs affecting lipid metabolism; cytostatic and immunosuppressive drugs; radiologic contrast media; drugs used in ocular treatment; drugs used in non-orthodox medicine; and miscellaneous drugs. (3118 Refs)

102. SEQUENTIAL VERSUS CONCOMITANT CHEMO-HORMONAL THERAPY IN BREAST CANCER.

Kumar KS, Vogel CL, Moore MR, Bartolucci AA
(c/o Vogel) Dept. Oncology, Univ. Miami Sch. Medicine, Miami, FL
Breast; 8(2):2-7 1982

Treatment with sequential or concomitant chemo-hormonal therapy was investigated in 44 patients (46-79 yr old) with metastatic breast cancer. None of the patients had been treated previously with hormonal therapy or chemotherapy. Twenty-one patients received sequential therapy consisting of diethylstilbestrol (DES: 5 mg po 3x/day for at least 2 mo or until disease progression occurred), withdrawal of DES, and chemotherapy followed when progression occurred [cyclophosphamide, 500 mg/square meter (m2); adriamycin, 50 mg/m2; and 5-fluorouracil, 500 mg/m2; iv every 3 wk for 9 courses (CAF)]. Concomitant therapy involved CAF on day 1, DES beginning on day 3, repeated every 3 wk for nine courses or until disease progression. Stable or responding patients were maintained on DES alone. If disease progression occurred, both DES and CAF were discontinued. The objective response rates were 56.5% for concomitant therapy and 42.8% for sequential therapy. Median duration of response was 9.8 mo for concomitant therapy and 7.7 for sequential therapy. Median survival was 20.4 mo for the concomitant group and 15.2 mo for the sequential group. No statistically significant differences were noted in overall response rate, remission duration, or survival between the two groups of patients. Six additional studies in which estrogens were combined with cytotoxic chemotherapy are reviewed. Little evidence was found that concomitant chemo-hormonal therapy for metastatic breast cancer provides an advantage over sequential therapy in patients chosen for initial hormonal therapy on the basis of receptor status, or on the basis of analysis of other prognostic variables. (73 Refs)

103. TREATMENT OF MALIGNANT BREAST TUMORS CONTAINING ESTROGEN RECEPTORS.

El'tsina NV
Moscow, USSR
Vopr Onkol; 28(4):95-102 1982

Literature data on the relationship between concentration of estrogen receptors (ER) and efficacy of hormonal therapy (HT) of breast cancer are reviewed. ER were detected in the cytosols of approx 60% of breast carcinomas, but only 55% of the ER-positive tumors were found to be sensitive to HT. These findings indicated that the ER assay per se is not sufficient for predicting response of breast cancer to HT and that it is essential to confirm the transport of ER complex into the cell nucleus and the binding of the complex with chromatin. The methods of predicting response to HT include determination of progesterone receptors (PR) and direct monitoring of ER complex in the nucleus and cytoplasm by the means of fluorescent microscopy. Most studies did not show a correlation between the ER status and response to chemotherapy. Recent studies showed the heterogeneity of estrogen-binding receptor proteins. (47 Refs) (In RUS)

104. SUPERIOR VENA CAVA SYNDROME IN CHILDHOOD AND ADOLESCENCE: A REVIEW OF THE LITERATURE AND REPORT OF THREE CASES.

Janin Y, Becker J, Wise L, Schneider K, Schwartz D, So H
(c/o Becker) 1300 Union Turnpike, New Hyde Park, NY, 11040
J Pediatr Surg; 17(3):290-295 1982

Obstruction of the superior vena cava is rare in childhood and adolescence. Its etiology is now mainly iatrogenic. Mediastinal tumors are the main primary causes of the superior vena cava syndrome (SVCS) in childhood and adolescence. The most common mediastinal tumors presenting with the SVCS are the lymph node tumors and especially the lymphosarcomas. About 50% of the mediastinal tumors are primary in the mediastinum. Early treatment is designed to cause a rapid shrinking of the tumor and should not be delayed by an overly diligent pursuit of the diagnosis. Treatment should consist of a combination of radiation therapy, chemotherapy, and steroids. Surgery should be limited to obtaining tissue for diagnosis, except when the tumor is localized to the mediastinum and is completely resectable. One hundred and seventy two children and adolescents with the SVCS are reviewed and three patients are added. (Author abstract) (83 Refs)

105. ENDOGENOUS HORMONES AS A MAJOR FACTOR IN HUMAN CANCER.

Henderson BE, Ross RK, Pike MC, Casagrande JT
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Cancer Res; 42(8):3232-3239 1982

Hormone-related cancers account for almost 30% of all cancer cases in the United States. Data from animal experiments and from epidemiological and endocrinological studies in humans support the hypothesis that the individual hormones which control normal growth of target organs can also create the proper conditions for neoplastic transformation. The concept that hormones can cause, ie, increase the incidence of, human cancer is most developed for the four hormone-related cancers which are numerically the most important, namely, breast, prostate, endometrium, and ovary. Even for these sites, large gaps remain in our knowledge of the responsible hormones and the conditions which create the optimal opportunity for carcinogenesis. Although scanty, the available epidemiological evidence also suggests a hormonal role in the pathogenesis of testis cancer, thyroid cancer, and osteosarcoma. We believe that the primary prevention of all these cancers will probably depend on modification of the factors which affect the secretion and metabolism of the responsible hormones rather than on control of exposure to classical exogenous initiators. (Author abstract) (129 Refs)

106. A REVIEW OF TEN CASES OF ALDOSTERONOMA. DIAGNOSTIC AND THERAPEUTIC CONCLUSIONS.

Parola JL, Berges C, Auvert J, Moretti JL, Meunier S, Lagrue G
(c/o Lagrue) Service de Nephrologie, Hopital Henri-Mondor, 51, avenue du Marechal-de-Lattre-de-Tassigny, 94010 Creteil, France
Sem Hop Paris; 58(25):1537-1542 1982

Ten patients with primary hyperaldosteronism resulting from a functioning adrenocortical adenoma were studied. The high incidence of hypertension and/or renal disease in the families of these patients suggests that hereditary factors play a part in the genesis of aldosteronomas. In patients with hypertension and hypokalemia the diagnosis of primary hyperaldosteronism is established by measurements of serum renin activity and serum aldosterone concentrations under normal conditions and during pharmacodynamic tests. The adenoma is demonstrated by radioactive iodocholesterol scintigraphy and computerized tomography. In nearly two-thirds of the patients, unilateral adrenalectomy is followed by complete definitive recovery. (Author abstract) (22 Refs) (In FRE)

107. PROLIFERATING BRENNER'S TUMOR AND HORMONE SECRETION.

Trevoux R, De Brux J, Cornet D, Scholler R
31, rue de L'Assomption, F75016 Paris, France
Gynecologie; 33(1/2):85-89 1982

The literature on proliferating Brenner's tumors is reviewed in connection with the 38th case of this tumor. The patient was a 56-yr-old menopausal woman in whom examinations for secondary hyperestrogenism led to the diagnosis of the tumor in the presence of palpable abdominal mass. The clinical and laboratory findings showed considerable estrogen secretion. Adnexectomy was performed; the tumor was diagnosed histologically in the surgical specimen. Proliferating Brenner's tumor is characterized by low grade malignancy. (14 Refs) (In FRE)

108. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

The possible association of oral contraceptives (OC) and menopausal estrogens (ME) on development of breast cancer is reviewed. The high incidence of breast cancer concurrent with extensive OC-ME usage, considered together with the relatively high hormone dependence of breast tumors and the placement of the breast as a target organ in the estrogen-progesterone hormonal pathways supports this association. Theories of the hormonal etiology involve estriol, progesterone, androgens, and the pineal gland; however, the specific hormonal etiology is unclear. Most studies have demonstrated significantly decreased risk of benign breast disease in women using OC. Since increased parity and early first birth are potentially protective conditions for breast cancer, OC, by simulating pregnancy, may exert a protective effect. The incidence of benign breast disease appears to be inversely related to the amount of progesterone in different OC. No significant overall increase in the risk of breast cancer has been demonstrated among users of OC. However, specific subgroups in which an increased risk was shown have been identified, including women with previous biopsy of benign breast disease. Evidence is available associating ME with an increased risk of endometrial carcinoma. Recent studies have demonstrated a positive association between ME and breast cancer. Caution is suggested in long-term use of OC and the continuous use of ME for periods greater than 10 yr should be reconsidered. (57 Refs)

109. THE PHYSIOLOGICAL IMPORTANCE OF THE COLONIC MICROFLORA.

Gustafsson BE
Dept. Germfree Res., Karolinska Inst., Box 60 400, S-104 01 Stockholm, Sweden
Scand J Gastroenterol [Suppl]; 17(77):117-131 1982

The present concept of the intestinal microflora has been reviewed with stressing the fact that it represents an entity with a wt comparable to one of the large organs of the body. It is composed of about 500 different strains, many of which as yet have not been isolated because 95% of them are anaerobic and fastidious in their growth requirements. The intimate relationship of the flora to the surface epithelium of the intestines and the Lieberkuhn's crypts are brought forward. The production of germfree animals is reviewed as an accounting of the most obvious differences between the germfree animal and its conventional counterparts, as far as gastroenterology is concerned. This includes the protective function of the normal intestinal flora, the cecum enlargement in germfree rodents, the influence of the flora on the metabolism of bilirubin, intestinal mucin, and pancreatic enzymes. Differences found in germfree animals due to the absence of the microbial flora related to the metabolism of fatty acids, bile acids, cholesterol and steroid hormones are also reviewed. The germfree animal has even proven to be an important research tool in such fields as carcinogenesis and studies of Crohn's disease and ulcerative colitis. There is need of a wider use of the germfree animal as a baseline in studies on the interference of the intestinal microbial flora with factors and conditions of great physiological and clinical importance. (Author abstract) (101 Refs)

OTHER RELATED STUDIES

110. TESTICULAR RELAPSE IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDREN.

Fujiu M, Bessho F
Dept. Pediatrics, Tokyo Univ., Tokyo, Japan
Rinsho Ketsueki; 23(1):33-39 1982

Occurrence of testicular relapse was studied in 51 boys with acute lymphocytic leukemia that were treated with chemotherapy. Induction chemotherapy consisted of either high dose steroid hormones (SH; prednisolone), high dose SH + vincristine (VCR), or normal dose SH + VCR. The testicular leukemia was treated with SH + VCR or chemotherapy and ipsilateral or bilateral testicular radiotherapy. Of the 51 patients, 43 achieved complete remission, and 17/43 had testicular relapse. There was no significant difference in the rates of testicular relapse between the group of patients who received the large dose SH and those who received the normal dose SH. However, the period of remission prior to relapse was significantly longer (av 53.1 mo vs 19.1 mo) for the patients given the large dose than those given the normal dose. Prognosis for testicular relapse was poor. A policy for prevention of testicular leukemia as the first relapse included detecting occult leukemic infiltration in biopsy specimens and early stage local treatment with reinduction therapy. (22 Refs) (In JPN)

111. EFFECT OF CRYOSURGERY OF PROSTATE IN SERUM GONADOTROPIN LEVELS IN PROSTATIC CANCER.

Washida H, Jinno H, Fushimi N, Watanabe H
Dept. Urology, Anjo Kosei Hosp., 12-38 Miyukihonmachi, Anjo, Aichi, 446, Japan
Cryobiology; 19(3):237-241 1982

Pituitary gland response to releasing hormone using the LH-RH loading test before and 4 wk after cryosurgery of the prostate was investigated in eight patients with advanced prostatic carcinoma. In pre- and postoperative comparisons of all patients, there were no significant differences detected before and after surgery. But pituitary response to the releasing hormone was compared before and after the surgery in each of the patients; in one, depression and facilitation of FSH and LH secretion, respectively, were observed and there was a variation in the response of gonadotropin in each patient. Although the number of observable patients is still too low to draw any definite conclusions from the test results, one possible interpretation is that cryosurgery of the prostate may influence hormonal secretion from the pituitary gland. (Author abstract) (19 Refs)

112. THE EFFECT OF BROMOCRIPTINE ON RENIN, ALDOSTERONE AND KIDNEY FUNCTION IN PATIENTS WITH ACROMEGALY AND PROLACTINOMA.

Jungmann E, Albus M, Bottger B, Magnet W, Althoff PH
Abteilung fur Endokrinologie, Zentrum der Inneren Medizin, Universitat Frankfurt am Main, Theodor-Stern-Kai 7, D-6000 Frankfurt/Main 70, W. Germany
Inn Med; 9(4):175-180 1982

Eleven patients with acromegaly and 4 with prolactinoma were given high dose therapy with bromocriptine (BC) over 1-5 yr. BC suppressed the aldosterone response to upright posture and furosemide and the furosemide-induced rise in plasma renin activity. BC increased cortisol and supine aldosterone levels in patients with normal renal function. BC decreased creatinine clearance (CC) to normal levels in patients with acromegaly and increased CC in patients with prolactinoma. In acromegaly BC improved adrenal function and CC by reducing levels of growth hormone. In prolactinoma BC increased CC by an adrenergic effect on renal perfusion. (15 Refs) (In GER)

113. CYCLIC OVARIAN FUNCTION AND BREAST CANCER.

Sherman BM, Wallace RB, Bean JA
Dept. Internal Medicine, Univ. Iowa, Iowa City, IA, 52242
Cancer Res; 42(8,Suppl):3286s-3288s 1982

We postulated previously that systematic differences in menstrual cycle length and/or variability might be used as indicators of underlying hormonal abnormalities that could help explain the endocrine biology of some breast cancer risk factors. In the present study, we prospectively and retrospectively analyzed menstrual cycle patterns in breast cancer cases and controls in two populations. No significant differences were found. This and previous studies emphasize that contemporary women have a long reproductive experience characterized by uninterrupted, regular menses, which is a condition of maximum ovulation potential and which contributes to estrogen stimulation over time. (Author abstract) (25 Refs)

114. AMINOGLUTETHIMIDE IN TAMOXIFEN-RESISTANT PATIENTS: THE MELBOURNE EXPERIENCE.

Murray RM, Pitt P
Endocrine Unit, Cancer Inst., Melbourne, Victoria, Australia
Cancer Res; 42(8,Suppl):3437s-3441s 1982

A group of 160 women with actively progressing metastatic breast cancer were treated with aminoglutethimide to induce medical adrenalectomy. The degree of adrenal suppression was monitored by measurement of dehydroepiandrosterone sulfate levels, and classification of response was carried out according to UICC criteria by two observers. Assessment of response is available for 136 patients, and of these 50 (36.7%) had an objective remission. In an additional 10 patients, the disease became static. Mean remission duration is 12.5 mo (range, 4 to 30). Forty-one patients had previously remitted to tamoxifen and then relapsed, and of these 22 (53.6%) experienced another remission with aminoglutethimide. Fifty patients had failed to respond to tamoxifen, and of these 16 (32%) had a remission with aminoglutethimide. In the 20 patients who did not receive tamoxifen and in the 25 whose response to it could not be classified, the remission rates to aminoglutethimide were 25 and 28%, respectively. The high remission rate to medical adrenalectomy in patients who have previously responded to tamoxifen makes it the treatment of choice in tamoxifen-responsive patients. (Author abstract) (6 Refs)

115. EFFECTS OF A PROLACTIN-SECRETING TUMOUR ON COPULATORY BEHAVIOUR IN MALE RATS.

Weber RF, Ooms MP, Vreeburg JT
Dept. Internal Medicine III, Univ. Hosp. Dijkzigt, Rotterdam, The Netherlands
J Endocrinol; 93(2):223-229 1982

The effect of the transplantable prolactin- and ACTH-secreting tumor 7315a on male copulatory behavior was investigated. Castrated tumor-bearing rats implanted with testosterone-filled capsules exhibited significantly longer latencies to first mount or intromission and to ejaculation than castrated control animals. In contrast to the number of intromissions, the number of mounts before ejaculation of the tumor-bearing rats was considerably increased. However, when castration was carried out in addition to adrenalectomy, the differences in copulatory behavior between tumor-bearing rats and control rats were no longer present. During the last tests for copulatory behavior the tumor-bearing rats had serum prolactin concentrations of more than 4,000 ng/ml while control rats had less than 100 ng/ml. Plasma testosterone levels produced by silicone elastomer capsules were neither affected by the presence of the tumor nor by adrenalectomy. It was concluded that hyperprolactinemia does not suppress the copulatory behavior of adrenalectomized rats. (Author abstract) (21 Refs)

116. 5-ACETOXY-2(3'-ACETOXYPHENYL)-3-ETHYL-1-METHYL-1H INDENE: A NEW MAMMARY TUMOR INHIBITING COMPOUND.

Schneider MR, Von Angerer E, Schonenberger H
(c/o Schonenberger) Inst. Pharmacy, Univ. Regensburg, Universitatsstrasse 31, 8400 Regensburg, W. Germany
Eur J Med Chem Chim Ther; 17(3):245-248 1982

The antitumor agents 5-acetoxy-1(3'-acetoxyphenyl)-3-ethyl-methyl-1H-indene (5AC) was synthesized by cyclization from 3,4-bis(3'-methoxyphenyl)-3,4-hexanediol. 5AC exhibits marked affinity to cytoplasmic estrogen receptor. 5AC inhibited the growth of dimethylbenzanthracene-induced, hormone dependent, mammary carcinoma in the SD-rat. (12 Refs)

117. PHARMACOKINETIC APPROACH TO THE SELECTION OF DOSE SCHEDULES FOR MEDROXYPROGESTERONE ACETATE IN CLINICAL ONCOLOGY.

Tamassia V, Battaglia A, Ganzina F, Isetta AM, Sacchetti G, Cavalli F, Goldhirsch A, Brunner K, Bernardo G, Robustelli Della Cuna G
Farmitalia Carlo Erba c/o Sacchetti, Funzione Medica Divisione Farmaceutica Italia, Via C. Imbonati, 24, I-20159 Milano, Italy
Cancer Chemother Pharmacol; 8(2):151-156 1982

The influence of bioavailability properties of im and po medroxyprogesterone (MPA) on drug blood level profiles during repeated administration is discussed. Such theoretical predictions were then compared with serum levels observed in patients with advanced breast cancer during treatment with high-dose MPA and with literature data. There was a progressive increase of MPA serum levels in nine patients treated im, up to 140-170 nanog (ng)/ml with a 1000 mg/day schedule and up to 35-70 ng/ml with a 1000 mg/wk schedule. During the 3 mo maintenance treatment with 500 mg im/wk serum levels were similar to or slightly higher than those reached at the end of the loading period. The MPA serum level profile in these patients was close to that expected theoretically. In six patients treated with MPA im, serum levels increased during 1-2 wk of treatment, then fluctuated around a steady state, close to theoretical predictions. The two dosage forms investigated were equivalent because the percentage of drug absorbed approached 100%. However, wide differences were observed among patients in favor of one formulation or the other. (17 Refs)

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STEROID HORMONE SYNTHESIS AND METABOLISM

1. METABOLISM OF TESTOSTERONE BY GR MOUSE MAMMARY TUMORS.

Abul-Hajj YJ, Kiang DT
Dept. Pharmaceutical Cell Biology, Univ. Minnesota, Coll. Pharmacy, Minneapolis, MN, 55455

Cancer Res; 42(9):3510-3513 1982

The metabolism of testosterone by GR mouse mammary tumors following serial transplantation was studied. Oophorectomized female recipients were maintained on estrone and progesterone (OEP) or without hormone maintenance (oophorectomized-only group) in order to assess whether the growth of the tumor was hormone dependent (HD) or hormone independent (HI). Tumors in the early generations of the OEP group were HD (generations 1 to 4), which became HI in the latter generations (G5 to G18). All tumors developed in the oophorectomized-only group (generations 1 to 18) were HI. All tumors investigated were capable of metabolizing testosterone to 4-androstenedione, 16alpha-hydroxytestosterone, 5alpha-dihydrotestosterone, 5alpha-androstanedione, and 5alpha-an-

HE 20.3173/2:

drostanediol. Total 5alpha-reduction in OEP group ranged between 50 and 60% of neutral metabolites in HD tumors and dropped to 13 to 28% in HI tumors (generations 5 to 18), similar to the activities (20 to 30%) of the HI tumors in the oophorectomized only group. Different patterns of estrogen synthesis were observed among these tumors. Although tumors showed the presence of appreciable amounts of estriol, estrone was synthesized only in 5 of the 9 HI tumors in the oophorectomized only group. The most striking contrast was that estradiol was synthesized by all HI tumors in the oophorectomized-only group and the OEP group but not in the HD tumors. (Author abstract) (13 Refs)

2. EFFECT OF DIET ON PLASMA AND URINARY HORMONES IN SOUTH AFRICAN BLACK MEN WITH PROSTATIC CANCER.

Hill P, Wynder EL, Garbaczewski L, Walker AR
Dept. Surgery, Medical Sch., Univ. Cape Town, Observatory 7925, Cape Town, South Africa
Cancer Res; 42(9):3864-3869 1982

Epidemiological evidence suggests that the incidence and death rate from prostatic cancer, an endocrine-associated disease, are related to environmental factors including diet. In this study, a comparison of serum and urinary levels of steroid hormones was carried out in healthy, elderly, rural South African black men on a vegetarian diet (a low-risk population), and a comparable group of men with prostatic cancer. In these prostatic cancer patients, plasma androgen levels decreased, while estrogen levels increased. Concomitantly, the androsterone:etiocholanolone ratio increased, and a greater proportion of estrogens was excreted as estriol. When transferred to a Western diet, plasma androgens showed a further decrease and a greater increase in estrone in prostatic cancer patients. In prostatic cancer patients, the total urinary androgen and estrogen levels were unaltered. However, in elderly healthy men, the Western diet decreased the excretion of estrogens and androgens. Thus, a Western diet supplemented the decrease in plasma androgens initially present in these patients. Evidence suggests that the decrease in plasma androgens increases the estrogen:androgen ratio, which may lead to hyperplasia of the prostatic ductal epithelia, a change enhanced by a Western diet. Changes in urinary steroid hormone levels in South African black patients comparable to those reported in white prostatic cancer patients indicate that hormonal changes must be related to several environmental factors, apart from diet. A simultaneous study of the steroid hormone composition of blood and prostatic fluid in this low-risk population is suggested. (Author abstract) (54 Refs)

3. ESTRADIOL, ANDROSTENEDIONE, TESTOSTERONE, AND DEHYDROEPIANDROSTERONE SULFATE IN THE OVARIAN AND PERIPHERAL BLOOD OF POSTMENOPAUSAL PATIENTS WITH AND WITHOUT ENDOMETRIAL CANCER.

Bremond AG, Claustrat B, Rudigoz RC, Seffert P, Corniau J
Clinique Gynecologique, Pavillion L, Hopital Edouard Herriot, Place d'Arsonval, 69374 Lyon Cedex 2, France
Gynecol Oncol; 14(1):119-124 1982

Estradiol (E), androstenedione (A), testosterone (T), and dehydroepiandrosterone sulfate (DHEAS) were determined in the plasma taken from the ovarian and cubital vein in endometrial cancer patients and controls. All the cases and controls experienced their menopause more than 4 yr before the study. The patients were matched for wt and height. No difference was found for T, A, and DHEAS in the peripheral blood between cases and controls. Nevertheless a statistically significant difference was observed for T and A, higher in the cases than in the controls: 4.38 +-1.32 vs 1.38 vs 0.51, for T and 5.69 +-1.65 vs 2.57 +-0.12 for A. Estradiol was higher in peripheral and ovarian blood of cancer cases when compared with the controls but the difference is not statistically significant. (Author abstract) (11 Refs)

4. FECAL NEUTRAL AND ACID STEROIDS AND B-GLUCURONIDASE AND 7ALPHA-DEHYDROXYLASE ACTIVITIES IN COLON CANCER AND CONTROL SUBJECTS (MEETING ABSTRACT).

Hathaway L, Ross JK, Leklem E
University of Vermont, Burlington, VT, 05405
Fed Proc; 41(3):354 1982

Neutral (NS) and acid (AS) steroids and 7 alpha-dehydroxylase (7alpha) and B-glucuronidase (BG) activities were determined in feces of 4 colon cancer patients, mean age (MA) 62 years and 6 controls, MA 49 years. For cancer patients, BG was 83 units/mg protein/hr and 7 alpha activity measured by production of deoxycholate (DCA) 11.9 and lithocholate (LCA) 2.1 nm/mg protein/hr. Controls had 201 units of BG and 5.7 nm DCA and 1.4 nm LCA for 7 alpha. While mean DCA and LCA levels of cancer subjects were higher than the controls as expected from other research, the differences were not significant due to wide individual variation. Certain changes in dietary fat and fiber are known to alter NS, AS, BG, and 7 alpha. Eighteen male controls (MA equals 24) on a test diet containing 2424 Cal, 81 g protein, 93 g fat, 720 mg cholesterol, and 3.6 g neutral detergent fiber were compared with 10 male and female controls (MA equals 27) on self-selected (SS) diets. For the test diet, mean total NS was 27.3 and mean total AS 13.3 mg/g dry wt feces. SS diets had mean total NS of 18.5 and mean total AS of 11.1 mg/g dry wt. Enzymes, quantified for 7 subjects on the test diet were 166 units of BG and 21.3 nm LCA and 12.3 nm LCA for 7 alpha. For SS diets BG was 151 units and 7 alpha was 23.3 nm for DCA and 8.1 nm for LCA. Only NS was significantly different between the diet groups. (no Refs)

DETECTION AND ASSAYS OF STEROID HORMONES AND METABOLITES

5. EFFECTS OF TAMOXIFEN ON THE SERUM LEVELS OF OESTROGENS AND ADRENOCORTICAL STEROIDS IN POSTMENOPAUSAL BREAST CANCER PATIENTS.

Wilking N, Carlstrom K, Skoldefors H, Theve NO, Wallgren A
Dept. Surgery II, Sabbatsberg Hosp., S-11382 Stockholm, Sweden
Acta Chir Scand; 148(4):345-349 1982

Peripheral serum levels of cortisol, dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHA-s), estradiol-17beta and total estrone were measured in 17 postmenopausal breast cancer patients and in age-matched healthy controls. In the breast cancer patients analyses were performed before and after 1, 2, 4, 8 and 12 wk of treatment with tamoxifen. Basal DHA levels were significantly higher in breast cancer patients than in controls; otherwise no significant differences were noted. Treatment with tamoxifen resulted in significantly elevated levels of cortisol throughout the period of treatment; this effect was probably solely due to an increase in transcortin levels. A transient but significant elevation in total estrone, probably related to liver function, was observed after 1 wk of treatment. No significant effects of tamoxifen were noted on serum DHA, DHA-s or estradiol-17beta. The results indicate that tamoxifen does not affect the adrenocortical steroid biosynthesis in postmenopausal women. The estrogenic effects of tamoxifen upon FSH, prolactin and the estrogen induced Pregnancy Zone Protein (PZP) in postmenopausal women, described in a previous communication from this group, are probably not due to any increase in the serum estrogens since this increase is transient and hardly impressive. The weak estrogenic effects of the tamoxifen-receptor complex itself may thus be sufficient to produce net estrogenic effects in subjects with low endogenous estrogens such as postmenopausal women. (Author abstract) (36 Refs)

6. THE SERUM LEVELS OF TESTOSTERONE AND PROLACTIN IN PATIENTS WITH PROSTATIC CARCINOMA TREATED WITH VARIOUS DOSES OF FOSTROLIN AND BROMOCRIPTIN.

Jeromin L
Dept. Urology, Inst. Surgery, Medical Acad., Lodz, Poland
Int Urol Nephrol; 14(1):51-56 1982

Forty-five patients with histologically proven prostatic carcinoma were treated with a combination of fostrolin (diethylstilbestrol diphosphate) and bromocriptine at various dose levels. High doses of fostrolin produced a rise in prolactin levels and serum testosterone levels. The optimal dose of fostrolin was 3 g total initial therapy delivered 250 mg/day iv on days 1, 2, 3, 4, 5, and 6, none on days 7 and 8, and 250 mg/day every day thereafter for a total of 20 days. Bromocriptine was given for 5 days in doses of 2.5 mg, tid, before onset of fostrolin treatment, and favorably affected clinical course of prostatic malignancy. (18 Refs)

7. BLOOD HORMONE LEVELS RELATED TO STAGES AND GRADES OF PROSTATIC CANCER.

Hoisaeter PA, Haukaas S, Bakke A, Hoiem L, Segadal E, Thorsen T
Section Urology, Dept. General Surgery, Univ. Bergen, 5016 Haukeland Sykehus, Bergen, Norway
Prostate; 3(4):375-381 1982

Blood hormone levels were determined in 100 patients (50-88 yr old) with different stages and grades of prostatic cancer. As to stages, 14 patients were in I, 25 in II, 25 in III, and 36 in IV. Within each stage, prostatic cancer was graded as highly differentiated carcinoma (50), moderately differentiated carcinoma (31), and poorly differentiated carcinoma (19). The blood samples were analyzed for follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), testosterone, estradiol, and sex hormone binding globulin (SHBG). Analysis of blood hormone levels in the patients with different stages and grades of prostatic carcinoma showed no specific hormonal pattern. The majority of patients had normal values of FSH, LH, and PRL, although PRL levels had a tendency to increase with increasing stage of the disease. Most of testosterone values were in a lower range of normal, compared with a significant number of estradiol levels that exceeded the normal range. Higher than normal SHBG values were observed in the patients with Stage I and Stage IV disease. (21 Refs)

8. SEX STEROID HORMONES LEVELS AND TESTICULAR ACTIVITY DURING HEPATOCARCINOGENESIS BY N-2-FLUORENYLACETAMIDE.

Lafaurie M, Aussel C, Castelli D, Krebs B, Stora C
INSERM U 210 (Laboratoire d'Histologie et d'Immunologie), 06034 Nice, France
Res Commun Chem Pathol Pharmacol; 37(1):49-63 1982

During hepatocarcinogenesis by N-2-fluorenylacetamide, the hormonal status of male Sprague Dawley rats is modified. The testes present a reduced activity which is evidenced by a decreased spermatogenetic activity accompanied by a drastic decrease of the plasma testosterone level. In contrast, plasma progesterone and estradiol-17beta levels were not modified despite the 80 fold augmentation of alpha-fetoprotein, an estrogen binding protein synthesized during liver carcinogenesis. (Author abstract) (27 Refs)

9. ANDROGEN LEVELS FOLLOWING ORCHIECTOMY (MEETING ABSTRACT).

Moss DI, Neerhut KJ
Ballarat Base Hospital, Ballarat, Victoria, Australia
Br J Urol; 54(1):73 1982

Free androgen levels are thought to reflect functional androgen activity more accurately than total androgen levels and they are easily measured by estimation of the Normalized Androgen Ratio (NAR). A normal range for this examination has previously been established. Free and total androgen levels were measured in 20 patients with untreated carcinoma of the prostate. Though the total levels varied considerably, free androgen levels were normal in all cases. Castrate levels of androgens were measured one month following bilateral orchiectomy. Serial measurements of androgens in this group of patients showed a rapid rall to castrate levels within 24 h following orchiectomy, being most evident in the protein-bound fraction. The timing of the fall corresponded with the prompt clinical response of bone pain to orchiectomy. A smaller group of patients being transferred from estrogen treatment to orchiectomy showed a range of variations. (1 Ref)

10. EXCRETION OF 17-KETOSTEROIDS AND CATECHOLAMINES DURING COMPLEX TREATMENT OF BREAST CANCER PATIENTS.

Godovanets BI
Dept. Surgery, Medical Inst., Ivano-Frankovsk, USSR
Klin Khir; (5):60 1982

The effect of complex radical treatment on excretion of 17-ketosteroids (17-KS) and catecholamines was studied in 249 patients with breast cancer (BC). Prior to being treated, the BC patients showed a stage-dependent increase in 17-KS excretion, decrease in norepinephrine excretion, and increase in epinephrine excretion. Radical treatment brought about normalization of the epinephrine excretion. (no Refs) (In RUS)

STEROID HORMONE RECEPTOR AND BINDING STUDIES

11. IDENTIFICATION OF A GLUCOCORTICOID RECEPTOR IN THE HUMAN LEUKEMIA CELL LINE K562.

Agius C, Gidari AS
(c/o Gidari) Dept. Pharmacology, State Univ. New York, Downstate Medical Center, 450 Clarkson Ave., Box 29, Brooklyn, NY, 11203
J Lab Clin Med; 100(2):178-185 1982

The binding of [3H]dexamethasone to the cytosol fraction prepared from the human leukemia cell line K562 was studied with a competitive binding assay. Specific, saturable binding was identified by incubating cytosol with increasing concentrations of [3H]dexamethasone in the presence and absence of nonlabeled dexamethasone. A Scatchard plot of the data was linear, suggesting the presence of a single class of binding sites with KD = 2.49 +-0.23 x 10(-8) M. the binding sites appear to be protein in nature, since specific binding was reduced by treatment of the cytosol with trypsin, pronase, and heat; neither DNase nor RNase affected the binding. Binding was also reduced in the absence of alpha-thioglycerol and in the presence of p-chloromercuribenzoate and N-ethylmaleimide, suggesting that optimal binding activity requires reduced sulfhydryl groups. The binding site appears to be specific for glucocorticoids as evaluated in competition studies. Finally, glucocorticoids were found to inhibit the clonal growth of K562 cells in vitro, suggesting a potential role for glucocorticoid binding sites in the modulation of K562 cell proliferation. (Author abstract) (33 Refs)

12. STEROID RECEPTORS IN HUMAN LUNG CANCER (MEETING ABSTRACT).

Thomas PA, Das Gupta TK, Beattie CW
Department of Surgery, University of Illinois, Chicago, IL
The Endocrine Lung in Health and Disease, June 2-4, 1982, Washington, D.C. The George Washington University Medical Center 31 pp., 1982.

The presence or absence of specific steroid hormone receptors may increase the potential for realizing clinically relevant data in histogenetically diverse lung malignancies. A preliminary prospective survey for the presence of high affinity steroid receptors in bronchogenic carcinoma cytosols was undertaken to correlate receptor incidence with histopathology. Thirty-one lung cancer tissue specimens were recovered from 27 men and 4 women. The sources of malignant tissue were the primary site, lung 24, metastatic deposits in lymph nodes 3, subcutaneous tissue 3 and bone 1. In addition to pathologic tissue, specimens of normal ventilating lung were recovered from 4 patients and assayed for receptor. Histopathological characterization of the malignancy was based on examination by light and electron microscopy. All specimens were obtained at the time of surgical removal, immediately frozen and stored at-80 C. Receptor assays were carried out for 16 hrs at 14 C using either dextran coated charcoal or protamine sulfate to separate bound from free ligand. Cytosols from 5 specimens of squamous carcinoma (series 2) and 4 normal lung specimens were also fractionated with ammonium sulfate (40%) prior to estrogen receptor assay. In addition, 20 mM molybdate ion was added to glucocorticoid receptor homogenization buffer prior to assay in a second series of squamous cell carcinomas and normal lung tissues to improve assay sensitivity. All binding data was analyzed according to the method of Scatchard. The results are tabulated. A value of greater than 3 fmol/mg cytosol protein was arbitrarily selected as a positive for receptor for all tumor specimens. No lower limit was set for normal lung tissue. Receptor binding was specific, saturable and indicative of a single class of high affinity (10(9), 10(10), M(-1)) sites for each class of steroid hormones. Glucocorticoid receptor incidence was limited (1/14) in squamous carcinomas prior to addition of molybdate ion to the assay buffer. In the presence of molybdate, it would appear that with the exception of small cell undifferentiated lung cancer a significant amount of this receptor is found in lung cytosols. There was also an apparent histopathology specificity for estrogen receptor in adenocarcinoma. (no Refs)

13. INTER-SITE VARIATION OF ESTROGEN RECEPTORS IN HUMAN BREAST CANCERS.

Izuo M, Iino Y, Takikawa H
Dept. Surgery, Gunma Univ. Sch. Medicine, 39-22, Showa-machi 3-chome, Maebashi 371, Japan
Jpn J Clin Oncol; 12(1):43-47 1982

Inter-site variations of estrogen receptors (ER) were investigated at multiple sites within large (greater than 3 cm in diameter) breast cancer tumors, and the relationship between levels of ER and cellularity (cell-stromal ratio) in the tumors was studied. Tumor specimens were obtained by radical mastectomy. The tumors were divided in half; one half was used in the ER assay, performed with sucrose gradient centrifugation, and one half was used for determination of cellularity by histological examination. Histological classification of the carcinoma consisted of five grades as follows: Grade I indicated a predominant stromal component; III indicated equal parts of tumor cells and stroma; V indicated a dominant tumor cell component; and II and IV were intermediate between Grade I and III and III and V, respectively. Inter-site variation in the presence or absence of ER was observed in 6/21 cases. However, ER values of the slices at the largest cross section reflected approximately the av value for the whole tumor, thus that value was regarded as representative of each tumor. Comparison of the presence of ER receptors and the Grade of cellularity (I-V) indicated that the more cellular portions have a higher frequency of ER. However, when the ER level was compared with the cell-stromal ratio classified by grade, the two factors had some correlation for Grade I-IV but not for the series as a whole. (5 Refs)

14. PLOIDY, PROLIFERATIVE ACTIVITY AND ESTROGEN RECEPTOR CONTENT IN HUMAN BREAST CANCER.

Raber MN, Bargolie B, Latreille J, Bedrossian C, Fritsche H, Blumenschein G
Oncology Div., Univ. Texas Medical Sch., 6431 Fannin St., Houston, TX, 77030
Cytometry; 3(1):36-41 1982

DNA flow cytometry was used in the analysis for ploidy and proliferative activity in 80 patients with breast cancer (43 primary, 37 metastatic). Estrogen receptor (ER) content was examined in 61 tumors (40 primary, 21 metastatic). Ploidy analysis showed that 68/80 tumors (65%) were hyperdiploid. A unimodal ploidy distribution was seen in 73 tumors; in 7 there were two distinct aneuploid subpopulations. The degree of ploidy abnormality was not related to extent of disease or menopausal status but was higher in poorly differentiated tumors. There was a higher proportion of diploid tumors in the ER-positive group (7/31 versus 3/30 ER-negative). DNA content was constant in biopsies from multiple sites in five patients with metastatic disease and in serial biopsies over the course of the disease. Proliferative activity, as indicated by percentage of cells in the S phase, was not related to extent of disease and menopausal status. High proliferative activity was more often associated with ER-negative tumors than ER-positive tumors, although there was a wide range of values in all subgroups. There was no significant increase in proliferative activity associated with increasing number of positive nodes at time of surgery or with increasing clinical stage. It is concluded that flow cytometric analysis of cellular DNA content provides a rapid means of quantitating ploidy and proliferative activity in human breast cancer. (40 Refs)

15. RELATIONSHIP BETWEEN THE CONTENT OF ESTROGEN AND PROGESTERONE RECEPTORS AND THE PATHOLOGICAL CHARACTERISTICS IN HUMAN BREAST CANCER.

Nishimura R, Misumi A, Kimura M, Tokunaga T, Akagi M
Second Dept. Surgery, Kumamoto Univ., Sch. Medicine, 1-1-1 Honjo, Kumamoto 860, Japan
Jpn J Surg; 12(3):191-197 1982

Prognostic significance of determination of estrogen receptors (ER) and progesterone receptors (PR) was studied in 124 women (27-88 yr old) with primary breast cancer. The ER and PR were analyzed using a dextran-coated charcoal competitive protein binding assay. The mastectomy specimens were measured, and the histological examination of primary tumors and of the axillary lymph nodes was performed. Of 124 tumors, 58.9% were ER-positive and 33.1% were PR-positive. The ER and PR contents were not correlated with the menopausal status, size of the tumor, involvement of the axillary lymph nodes, or histological type of the tumor. The ER and PR status showed significant correlation with the histological grade: 78.2% of well differentiated Grade I tumors and 60.0% of Grade II tumors were ER-positive, compared with 27.5% of Grade III tumors. Correspondingly, 47.8% of Grade I tumors and 35.0% of Grade II tumors were PR-positive, compared with 6.8% of Grade III tumors. The tumors with little lymphoid infiltration had higher ER and PR levels than the tumors with abundant lymphoid infiltration. (26 Refs)

16. LYMPHOCYTE REACTIVITY TO MITOGENS AND TUMOR SEX STEROID RECEPTORS IN BREAST CANCER PATIENTS (MEETING ABSTRACT).

Kastelan M, Rudolf M, Hrsak M, Stojkovic R, Gamulin S
Department of Clinical Oncology, University of Zagreb, Zagreb, Yugoslavia
Fifth European Immunology Meeting, June 1-4, 1982, Istanbul, Turkey. Turkish Society of Immunology 354 pp., 1982.

In 60 breast cancer patients in stage I and II the blastogenic transformation of peripheral blood lymphocytes after Phytohemagglutinin (PHA) Concanavalin A (Con A) and Pokeweed mitogen (PWM) stimulation were assayed and estrogen (ER) and progesterone (PgR) receptor concentrations in tumor cytosol were measured. The blastogenic responses to mitogens were done according to Hartzman et al. For ER and PgR assays we used dextran coated charcoal method based on that of McGuire and Horwitz and McGuire. A negative correlation between lymphocyte reactivity to the mitogens and tumor steroid receptor concentration was found. The lymphocyte response to the mitogens in the patients with ER-PgR- tumors was significantly higher than in those with tumors either Er+PgR- or or ER-PgR+ or ER+PgR+. There was also a negative correlation between lymphocyte response to PHA and either ER or PgR concentration in the tumors. These results suggest that the presence of steroid receptors in tumor cells may be associated with the depression of immunological reactivity in breast cancer patients. (3 Refs)

17. CYTOCHEMICAL ANALYSIS OF HUMAN BREAST CANCER WITH FLUORESCENT SEX-STEROID CONJUGATES. COMPARISON WITH BIOCHEMICAL ASSESSMENT OF OESTROGEN RECEPTORS.

Danguy A, Leclercq G, Pattyn G, Devleeschouwer N, Pasteels JL, Heuson JC
Lab. Histology, Faculty Medicine, 1000 Brussels, Belgium
Anticancer Res; 1(6):361-366 1981

Two hydrophilic steroid reagents, 17 beta-estradiol-6-carboxymethyloxine-bovine serum albumin-fluorescein isothiocyanate (E2-BSA-FITC) and 11alpha-hydroxyprogesterone hemisuccinate-bovine serum albumin-tetremethylrhodamine isothiocyanate (Pg-BSA-TMRITC) were used to study cytochemical steroid binding activity of human mammary cancer cells MCF-7 and EVSA-T. In most samples, epithelial cells exhibited a cytoplasmic fluorescence with both reagents. In 13 tumors, a nuclear and cytoplasmic fluorescence was observed with E2-BSA-FITC, and in 6 only a nuclear fluorescence was observed. Nuclear fluorescence was never observed with Pg-BSA-TMRITC. Connective tissue, myoepithelial cells, or vascular smooth cells were always negative. Most cells positive for E2-BSA-FITC were also stained with Pg-BSA-TMRITC. A total absence of correlation was observed between the results obtained by histochemical and biochemical methods. In the competitive inhibition test of [3H]estradiol binding, only low dilution of the E2-BSA-FITC produced a slight inhibition. The result indicated that the preparation had a very low binding affinity for estrogen (ER). The identical staining pattern of MCF-7 and EVSA-T cell lines indicated that the reagents were inefficient to differentiate between ER-positive and ER-negative culture. (21 Refs)

18. ESTROGEN RECEPTORS IN HUMAN BREAST CANCER. I. SPECIFICITY OF THE HISTOCHEMICAL LOCALIZATION OF ESTROGEN RECEPTORS USING AN ESTROGEN-ALBUMIN FITC COMPLEX.

van Marle J, Lindeman J, Ariens AT, Labruyere W, Van Weeren-Kramer J
Pharmacological Lab., Univ. Amsterdam, Polderweg 104, NL-1093 KP Amsterdam, The Netherlands
Virchows Arch [Cell Pathol]; 40(1):17-25 1982

An investigation of the specific localization of estrogen receptors in frozen sections of mammary tumors using an estrogen-BSA-FITC complex is presented. The results are discussed in relation to the existing literature. Although the fluorescence is certainly not due to interaction with Type I receptors, the reaction is not as non-specific as is suggested sometimes in the literature. It is likely that Type II receptors are involved, which are probably localized at the same site as Type I receptors. (Author abstract) (23 Refs)

19. ESTROGEN RECEPTORS IN HUMAN BREAST CANCER. II. CORRELATION BETWEEN THE HISTOCHEMICAL METHOD AND BIOCHEMICAL ASSAY.

Meijer CJ, Van Marle J, Persijn JP, Van Niewenhuizen W, Baak JP, Boon ME, Lindeman J
Dept. Pathology, S.S.D.Z., Reynier de Graefweg 7, NL-2625 AD Delft, The Netherlands
Virchows Arch [Cell Pathol]; 40(1):27-37 1982

The present study defines criteria for determining the presence of estrogen-receptors in human breast carcinomas demonstrated by a histochemical assay using 17beta-estradiol-carboxymethyl-oxim-bovine serum albumen-FITC. The criteria were:

(1) the percentage of cells showing fluorescence; (2) the intensity of the fluorescence observed, and (3) the percentage of epithelial structures in tissue specimens. Using these predefined criteria in 132 human breast carcinomas a 91.6% agreement was found between the results of the histochemical assay and those of the biochemical Charcoal method. The main causes of disagreement (7 of the 11 cases) were sampling errors between the tissue specimens used for the histochemical and biochemical assay, and an insufficient percentage of epithelial structures (less than 15%) to allow biochemical identification of estrogen receptor activity. In the hands of pathologists with experience in the field of histochemistry this histochemical assay may be the method of choice for the assessment of estrogen receptors. (Author abstract) (16 Refs)

20. ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER IN BLACK AMERICANS. CORRELATION OF RECEPTOR DATA WITH TUMOR DIFFERENTIATION.

Mohla S, Sampson CC, Khan T, Enterline JP, Leffall L, White JE, Gabriel BW, Hunter JB
Howard Univ. Cancer Center, 2041 Georgia Ave., Northwest, Washington, DC, 20060
Cancer; 50(3):552-559 1982

It has been observed that 60-70% of breast cancer patients have estrogen receptors (ER) and that nearly two-thirds of such patients respond favorably to endocrine therapy. Cytosolic ER and progesterone receptors (PgR) have been evaluated in the current study, among 146 black women with breast cancer in order to determine whether the distribution of ER and PgR differs from the national normal. The results showed following trends that were similar to reports from other institutions: (1) postmenopausal patients and primary tumors showed higher ER positivity than premenopausal patients and metastatic sites, respectively; (2) a significant correlation between the ER positivity and tumor grade; and (3) a higher PgR positivity in ER-positive patients than in ER-negative patients. However, statistically significant differences were observed in three parameters when compared to reports from other institutions on white patients: (1) a low incidence of ER-positive (46%) and high incidence of ER-negative (42%) tumors; (2) a higher incidence of poorly differentiated (55.5%) and a lower incidence of well differentiated (5.5%) tumors; tumor grade was independent of age, menopausal status, histopathology and stage; and (3) a higher percentage of patients discovered at a more advanced stage of the disease. The clinical implications of these results in explaining the relatively poorer survival of black women with breast cancer compared to whites is discussed. Whether this high incidence of PD tumors and thus a high incidence of ER negativity is due to ethnic differences and/or environmental and other factors remains to be elucidated. (Author abstract) (48 Refs)

21. TUMOR HISTOLOGY AND STEROID RECEPTORS IN BREAST CANCER.

Jakesz R, Reiner A, Bieglmaier C, Reiner G, Krisch K, Kolb R, Spona J, Schemper M
I. Chirurgische Univesitats-Klinik Wien, Alsterstrasse 4, A-1090 Wien, Austria
Onkologie; 4(2):73-75,77-78 1981

In specimens of 115 patients with breast cancer four tumor parameters (tumor size, tumor border, nuclear grade, lymphocytic stromal reaction) three features of regional lymph nodes (sinus histiocytosis, T-cell reaction, lymph node metastases) and estrogen and progesterone receptors were determined. A strong sinus histiocytosis and T-cell reaction could be verified mainly in metastases in free lymph nodes. The steroid receptor content does not correlate with histological parameters. (Author abstract) (46 Refs) (In GER)

22. CORRELATION OF MEAN NUCLEAR AREA WITH ESTROGEN RECEPTOR CONTENT IN ASPIRATION CYTOLOGY OF BREAST CARCINOMA.

Mossler JA, McCarty KS, Woodard BH, Mitchener LM, Johnston WW

(c/o McCarty) Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710

Acta Cytol (Baltimore); 26(4):417-421 1982

Thin needle aspirates of 42 consecutive breast carcinomas were obtained at the time of excisional biopsy. Nuclear diameters of 100 cells from each case were measured, and the nuclear areas were calculated. The concomitantly acquired histologic sections were reviewed and assigned a histologic grade according to the National Surgical Adjuvant Breast Project protocol no 4. Estrogen receptor (ER) content was analyzed by both the DCCA and SDGA techniques. The ER content of each case was then compared to both the mean nuclear area of the cells on the cytologic smears and the histologic grade. All 16 cases with mean nuclear areas of less than 60 sq um contained significant levels of ER (greater than 10 fmol/mg protein), as did 6 of 11 cases with nuclei between 60 and 90 sq um. Only 5 of 15 cases with nuclei larger than 90 sq um contained significant ER levels. Comparison of the sensitivity, specificity and predictive values of both techniques suggests that a quantitative assessment of nuclear area in cytologic thin needle aspirates correlates more closely with ER content then does histologic grading. (Author abstract) (16 Refs)

23. QUANTITATIVE ESTROGEN RECEPTOR VALUES AND GROWTH OF CARCINOMA OF THE BREAST BEFORE SURGICAL INTERVENTION.

Antoniades K, Spector H

Dept. Pathology, Crozer-Chester Medical Center, Chester, PA, 19013

Cancer; 50(4):793-796 1982

Quantitative estrogen receptor (ER) values in patients with breast carcinoma were correlated with the natural history of the disease before surgical intervention. The natural history was expressed as an index of growth. This was determined as a ratio between tumor size (centimeters) and duration of symptoms (wk). An inverse correlation was found between amount of ER and growth. Tumors with high positive (above 101 fmol/mg protein) ER values had grown significantly slower (p less than 0.05) than tumors with low positive (below 50 fmol/mg protein) or negative ER values. These two latter groups had a similar natural history. Recognition of the fact that there is slow growth in carcinomas with high ER as well as of the fact that growth is as rapid in carcinomas with low ER levels as it is in carcinomas with negative ER values, demonstrates the importance of quantitative ER determinations, their prognostic value, and their usefulness in planning therapy. (Author abstract) (23 Refs)

24. THE SIGNIFICANCE OF QUANTITATIVE BIOLOGICAL CELL PARAMETERS IN THE HANDLING OF MAMMARY CARCINOMA.

Theve NO, Azavedo E, Blomstedt B, Wilking N, Auer GU
Dept. Surgery, Sabbatsberg Hosp., Stockholm, Sweden
Acta Chir Scand; 148(3):239-241 1982

Recent work has shown that in breast cancer patients DNA measurements and estrogen receptor (ER)-analysis can contribute valuable information in the judgement of prognosis and choice of therapy. We report a case of advanced breast carcinoma with extensive liver metastases which clinically was regarded as beyond all therapeutic possibilities. Liver metastases were diagnosed first. Some time later a breast carcinoma was detected which was suggested to be the primary malignancy. Since high ER-values were demonstrated in the breast carcinoma, anti-estrogen therapy was given on trial. After 3 mo the tumor mass in the liver had drastically diminished and today, more than 4 yr after diagnosis, the patient is free from symptoms and doing excellently. A retrospective, microspectrophotometric DNA analysis in both the breast carcinoma and the liver metastasis showed DNA distribution patterns with nearly all the carcinoma cells exhibiting DNA values in the normal diploid region. This type of DNA profile has previously been shown to be correlated with good prognosis. We conclude that quantitative parameters such as DNA- and ER-content can give prognostic and therapeutic information over and above that furnished by clinical stage and morphological criteria. (Author abstract) (15 Refs)

25. THE IMPORTANCE OF RAPID FREEZING OF BREAST TUMOURS FOR THE ACCURATE DETERMINATION OF CYTOPLASMIC OESTRADIOL RECEPTOR (ER) STATUS IN PRIMARY BREAST CANCER (MEETING ABSTRACT).

Bishop HM, Poole T, Blamey RW, Nichsolson RI, Griffiths K
City Hospital, Nottingham, England
Clin Oncol; 8(1):86 1982

The ER status of primary breast cancer provides information on prognosis and endocrine dependence. The object of this study was to determine the importance of the method of taking tumor for assay. The tumors were taken from a series of women undergoing mastectomy for primary operable breast cancer. On removal the breast was passed immediately to a technician waiting in the operating theatre. Two opposing quarters of the tumor were dissected free and each packed in a double layered plastic bag. One quarter was immediately placed in a flask of liquid nitrogen, the other was kept for 1 hr at room temperature before freezing in liquid nitrogen. Thereafter both specimens were handled identically. ER status was determined using the Dextran Coated Charcoal method: ER positive result was taken as more than 5 femtomoles ER protein/mg cytosol protein. Thirty-eight tumors were studied. In Immediate freezing: ER positive 25 and In Late Freezing: 20 remained positive and 5 converted to negative; In immediate freezing: ER negative 13, and in Late freezing: all 13 remained negative. For accurate ER estimation it is essential that breast tumors are frozen in liquid nitrogen immediately after removal of the breast and not after waiting until the operation is completed. (no Refs)

26. CLINICAL APPLICATION OF HORMONE RECEPTORS IN DISEASES OF THE BREAST.

Gomez Pastrana F, Gonzalez Gancedo P, Calero F, Inocente JM
Departamento de Obstetricia y Ginecologia, Ciudad Sanitaria de la Seguridad Social 'La Paz', Madrid, Spain
Acta Obstet Ginecol Hisp Lusit; 30(1):47-52 1982

Estrogen receptors were determined in 97 patients with histologically confirmed breast cancer. The test results were positive (estrogen receptor levels exceeding 5 femtomoles/mg protein) were in 56/97 patients, negative in 41/97. The results were positive in 3/5 patients in clinical Stage I, in 35/48 in II, in 14/36 in III and in 2/6 in IV. The incidence of positive test results was found to be significantly higher in the patients in Stage I + II than in those in III + IV (p less than 0.02). The estrogen receptor levels averaged 31.6 femtomoles/mg in the menopausal women and 15.9 femtomoles/mg in the premenopausal women; the difference between the two groups was statistically significant (p less than 0.001). The retrospective analysis of the incidence of recurrences during the first 15 mo after treatment showed that recurrences were more frequent among the estrogen receptor-negative patients than among the positive patients (17.8% vs 10.8%), but the difference was not significant statistically. (8 Refs) (In SPA)

27. OESTROGEN RECEPTOR (ER) STATUS OF PRIMARY BREAST CANCER AND RESPONSE OF SECONDARY DISEASE TO ENDOCRINE THERAPY (MEETING ABSTRACT).

Campbell FC, Blamey RW, Morris AH, Nicholson RI, Griffiths K
Department of Surgery, Nottingham City Hospital, Nottingham, England
Clin Oncol; 8(1):85 1982

The relationship between ER status of breast cancer and response to endocrine treatment is well established. Reports have dealt largely with ER assays of secondary tumor, and data relating response of secondaries to ER status of the primary tumor are scant. A possible objection to ER of primary used thus is that ER positive primaries may have ER negative secondaries. In this study ER of primary cancer was measured in 526 patients. Metastases developed in 95 who were treated by endocrine therapy. ER was also measured in secondary tissue in 29 patients of whom 20 received endocrine treatment (premenopausal--oophorectomy; post-menopausal--Tamoxifen 20 mgm bd). Of 24 patients with ER measurements of both primary and secondary cancer, the initial status changed in 6. Response to treatment was defined by UICC criteria with a minimum duration of 6 months. ER status changes between primary and secondary cancer in up to 25% of cases. ER of the primary (which is an ample source of tissue) appears a very good predictor of response of subsequent secondary cancer to hormone therapy. (2 Refs)

28. PROSTAGLANDIN E2 SYNTHESIS BY TUMOUR EPITHELIAL CELLS AND OESTROGEN RECEPTOR (ER) STATUS OF PRIMARY BREAST CANCER (MEETING ABSTRACT).

Campbell FC, Haynes J, Evans DF, Mumford C, Blamey RW, Elston CW, Nicholson RI
City Hospital, Nottingham, England
British Association of Surgical Oncology Summer Meeting, July 15-16, 1982, Portsmouth, England British Association of Surgical Oncology; 1982

ER positive breast cancer preferentially metastasize to bone. Prostaglandin E2 (PgE2) is synthesized by breast cancers and potentiates bone resorption in vitro. This study investigates the relationship between ER status and PgE2 synthesis in breast cancer cells. PgE2 was measured by radioimmunoassay in 75 primary breast cancers: a) After ethanol inhibition of further prostaglandin (Pg) production - 'Basal Pg'. b) After stimulating Pg production with excess Arachidonic Acid - 'Total Pg'; 'Total' minus 'Basal' equals 'Synthesized Pg'. In order to relate Pg production to breast cancer cells, measured PgE2 values have been corrected for the epithelial cellularity of each tumor. Corrected PgE2 equals Measured PgE2 x 100 Actual (%) Cellularity. (no Refs)

29. AN IN VITRO ASSAY OF TAMOXIFEN SENSITIVITY IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Holt S, Croton R, Prichard J, Leinster S, George W, Nicholson R, Griffiths K
Department of Surgery, University of Liverpool, Liverpool, England
British Association of Surgical Oncology Summer Meeting, July 15-16, 1982, Portsmouth, England British Association of Surgical Oncology; 1982

Estrogen receptor status (ER) is acknowledged as a sensitive predictor of response to hormone therapy in advanced breast cancer. Nevertheless 40% of ER+ve tumors will fail to respond and therefore an in-vitro test to measure hormone responsiveness would be valuable. Twenty-one women with advanced breast cancer accessible to biopsy were studied. A sample of tumor was removed, assayed for ER status, and the in vitro effect of Tamoxifen on 3H uridine uptake was measured. After treatment with Tamoxifen subsequent clinical response, according to UICC criteria, was related to the in vitro findings. Median followup was 8 months. Of 11 tumors showing in vitro inhibition, 9 responded clinically to Tamoxifen. Ten tumors showed no inhibition in vitro, and 7 of these were clinically unresponsive. The sensitivity of 75% and specificity of 78% compare favorably with the predictive value of ER. Furthermore, 4 ER+ve tumors were unresponsive clinically to Tamoxifen and this was detected by the assay in 3. Conversely, 2 ER-ve Tamoxifen responsive tumors were identified by the assay. These results show that this simple in vitro test is valuable in identifying those women with advanced breast cancer who will respond to Tamoxifen. (no Refs)

30. ISOLATION AND CHARACTERIZATION OF A SERIALLY CULTIVATED, NEOPLASTIC, EPITHELIAL CELL LINE FROM THE N-NITROSOMETHYLUREA INDUCED RAT MAMMARY ADENOCARCINOMA.

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American Health Foundation, Naylor Dana Inst. Disease Prevention, Dana Road, Valhalla, NY, 10595
In Vitro; 18(6):565-575 1982

A new in vitro model for human breast cancer is described. Derived from an N-nitrosomethylurea (NMU) induced rat mammary adenocarcinoma, this serially cultivated cell line has been demonstrated, by a variety of criteria, to be an authentic neoplastic, rat mammary epithelial cell line. The criteria used include morphological and growth characteristics; the presence of specific cell surface antigens; steroid hormone receptors; hormone responsiveness; casein production; karyotype and isoenzyme profile analysis; anchorage independent growth and oncogenicity. Inasmuch as the NMU cell line possess high concentrations of glucocorticoid and androgen receptors, it may provide a useful model for study of the action of these hormones in human breast cancer. In addition, the NMU line may serve as a valuable in vitro model in which to assess the effects of a variety of endogenous and exogenous agents known to influence mammary tumor growth in vivo, including drugs, nutrients, and growth factors. (Author abstract) (44 Refs)

31. ROLE OF ESTROGEN AND PROLACTIN IN THE GROWTH AND RECEPTOR LEVELS OF N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS.

Manni A, Rainieri J, Arafah BM, Finegan HM, Pearson OH
Dept. Medicine, Div. Endocrinology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Cancer Res; 42(9):3492-3495 1982

Forty-eight of 81 (59%) of N-nitrosomethylurea-induced rat mammary tumors regressed in av to almost one-half of the original size 10 days after ovariectomy (ovax) (hormone responsive), while 33 remained essentially unchanged (hormone resistant). At 20 days after ovax, further decline in hormone-responsive tumors was observed when the rats were treated daily with 0.9% NaCl soln on the 10th day after ovax. Treatment for the same length of time with estrogen either alone or in combination with bromocriptine (to effectively suppress serum prolactin level) prevented tumor regression in hormone-responsive tumors. A similar effect was observed when rats were treated with perphenazine (to stimulate endogenous prolactin secretion) either alone or in combination with the antiestrogen tamoxifen. Estrogen receptors (ERs) significantly declined after ovax. Treatment with estrogen or perphanazine did not have any significant effect on ER levels. Progesterone receptors (PGRs) became virtually undetectable after ovax. Treatments with estrogen, estrogen plus bromocriptine, and perphenazine plus tamoxifen but not perphenazine alone were able to partially restore PGRs although this effect was of borderline statistical significance. ER and PGR levels were not significantly different between hormone-responsive and -resistant tumors within each group. We conclude that both estrogen and prolactin play a role in the growth of the N-nitrosomethylurea-induced rat mammary tumor. Changes in ER and PGR levels did not correlate with tumor growth under the present experimental conditions. (Author abstract) (18 Refs)

32. LOW BINDING OF THE ESTROGEN RECEPTOR FROM MAMMARY TUMORS TO HEPARIN-SEPHAROSE.

Michel O, Leclercq G, Toma S
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Anticancer Res; 1(6):403-408 1981

Chromatographic behavior of estrogen receptor (ER) from immature uterus, lactating mammary glands, and mammary tumors of the rat on heparin-Sepharose (h-SP) was studied. Investigations are presented of the interaction of h-SP with mammary tumor ER from various sources: 10 7,12-dimethylbenz[a]anthracene (DMBA)-induced rat tumors, 7 MXT transplantable mouse mammary tumors, 2 MCF-7 cells, and 3 samples of pooled human breast cancers. The major part of all the tumor ER eluted within the first peak with the material that did not bind to the matrix. Only two tumors (1 DMBA-induced and 1 MXT) displayed an elution pattern indicative of strong binding. ER strongly interacted with the h-SP matrix during a short incubation period (0-30 min). The progressive loss of binding capacity to h-SP after long-term incubation was due to the action of a cytoplasmic factor that did not interact with the h-SP. Incubation of the cytosol with h-SP at 20 C was found to reduce the binding capacity of ER to the matrix suggesting that an increase in temperature activates the cytoplasmic factor responsible for ER dissociation. Purification by ammonium sulfate precipitation suppressed the progressive dissociation of ER from the matrix. The addition of various proteolytic inhibitors to various proteolytic mammary tumor cytosols failed to stabilize the association of ER to h-SP. (12 Refs)

33. DESIGN, SYNTHESIS AND BIOLOGICAL PROPERTIES OF ESTROGEN RECEPTOR BINDING BREAST TUMOR LOCALIZING AGENTS.

Senderoff SG
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(9):3696-B 1982

Several steroidal estrogens halogenated on the D-ring were synthesized and subjected to preliminary in vitro evaluation for usefulness as estrogen receptor binding radiopharmaceuticals. Two of these compounds, 16 alpha-bromoestradiol-17beta and 11 beta-methoxy-16-alpha-bromoestradiol-17beta exhibited high binding affinity for the estrogen receptor, and were chosen for development into radiopharmaceuticals with the potential to act as breast tumor localizing agents. They were used to image DMBA induced mammary adenocarcinoma in mature female rats with the use of the Anger scintillation camera. [77Br]-16 alpha-Bromoestradiol-17 beta was further evaluated (dosimetry, pharmacology) for use as scintigraphic agent in humans. This compound was used to obtain an image of a primary human breast tumor that was shown to contain high levels of estrogen receptor upon removal. These results are the first example of scintigraphic imaging of estrogen receptor containing mammary tumors in animals or humans utilizing a receptor binding radiopharmaceutical. (no Refs)

34. ARE RECEPTORS TO BILE ACIDS PRESENT IN HUMAN COLORECTAL CANCER? (MEETING ABSTRACT).

Summerton J, Flynn M, Cooke T, Taylor I
University of Surgical Unit, Southampton University Medical School, Southampton General Hospital, Southampton, England
British Association of Surgical Oncology Summer Meeting, July 15-16, 1982, Portsmouth, England British Association of Surgical Oncology; 1982

Although studies have identified bile acids as a probable etiological factor in the development of colorectal cancer the exact nature of this involvement is unclear. A preliminary investigation has been performed to determine whether receptors specific to secondary bile acids (deoxycholic acid) exist in colorectal cancer tissue. Forty-three samples of human colorectal cancer removed at laparotomy and 33 samples of adjacent colon were studied. Bile acid receptor status was analyzed by a modified estrogen receptor method using 14C-deoxycholic acid. Samples of normal stomach and gastric cancer were assayed in an identical manner. Twenty-five point 6 percent of colorectal cancers had specific receptors to deoxycholic acid. They were not identified in benign colorectal tumors or gastric malignancy. Only 1 sample of normal colon contained receptors (p less than 0.01). Metastatic colorectal cancer did not possess specific receptors (5 patients). Further studies have been performed to confirm the specificity of deoxycholic binding. Autoradiographs using 3H-deoxycholic acid demonstrated specific labelling and Scatchard analyses have been performed. In conclusion initial studies have demonstrated specific receptors to deoxycholic acid in human colorectal cancer. It is possible that this binding influences the development and growth of large bowel cancer. (2 Refs)

35. ESTRADIOL AND PROGESTIN RECEPTORS, 17-BETA-HYDROXYSTEROID-DEHYDROGENASE AND HISTOPATHOLOGIC GRADE IN ENDOMETRIAL CARCINOMA.

Ciuffi M, Savino L, Santini D, Buzzoni P, Scarselli G, Mazzei T
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Tumori; 68(3):217-221 1982

The possible correlations between steroid receptor systems, 17-beta-hydroxysteroid-dehydrogenase (17-beta-HSD) and histopathologic examinations were investigated. The well-differentiated tumors showed higher steroid receptor and 17-beta-HSD values than undifferentiated carcinomas. The steroid receptors did not present a statistically significant correlation with 17-beta-HSD. Nevertheless, some neoplastic endometria (29%) show higher values of progestin receptors and 17-beta-HSD, with a progestin:estrogen receptor ratio greater than one. (Author abstract) (15 Refs)

36. ESTROGEN RECEPTORS IN HUMAN UTERINE ADENOCARCINOMA: CORRELATION WITH TISSUE DIFFERENTIATION, VAGINAL KARYOPYCNOTIC INDEX, AND EFFECT OF PROGESTOGEN OR ANTI-ESTROGEN TREATMENT.

Billiet G, De Hertogh R, Bonte J, Ide P, Vlaemynck G
Gynecological Cancerology Dept., K.U.L. Leuven, UCL Brussels, Belgium
Gynecol Oncol; 14(1):33-39 1982

Estrogen receptor levels were measured in the cytosol of uterine adenocarcinomas obtained by endometrial biopsy in 37 postmenopausal women. The karyopycnotic index was determined individually by vaginal smear. It was considered estrogenic when superior to 5% (KI+). The histologic characteristics of the tumors were classified as well (D+) or poorly (D-) differentiated. The receptor level was highest in D+KI- tumors (103 +-19 (SEM) fmole/mg protein), intermediate in D+KI+ tumors (44 +-12), and lowest in D- tumors (25 +-10). During medroxyprogesterone acetate (MPA) treatment, the receptor level dropped rapidly in D+ tumors (from 87 +-14 to 16 +-5) and remained low in D- tumors (25 +-10 to 1 +-1). Tamoxifen (T) treatment also produced a reduction in the receptor levels: in D+ tumors to 1 +-1 and in D- tumors to 6 +-2. In conclusion, high receptor levels in cytosol of D+ tumors as well as the significant reduction under MPA or T treatment suggest the persistence in these tumors of hormonal regulatory mechanisms. Estrogenic impregnation of the patient should, however, be taken into account to differentiate between the hormone-sensitive D+KI+ tumors and the receptor-poor D- tumors. (Author abstract) (23 Refs)

37. INTERRELATIONS BETWEEN FREE, OCCUPIED CYTOSOL AND NUCLEAR ANDROGEN RECEPTOR IN HUMAN PROSTATE (MEETING ABSTRACT).

Mobbs BG, Johnson IE, Connolly JG
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

In an investigation of prostatic androgen receptor (AR) during the course of prostatic carcinoma, we have assayed cytosol AR (both free sites and those bound by endogenous androgen) and nuclear AR in untreated, orchiectomized and/or estrogen-treated patients. AR was quantitated using 3H-R1881 as ligand under conditions which conserve AR and prevent 3H-R1881 binding to progesterone receptor. Results from the cytosol assay confirmed our earlier work obtained with the protamine sulphate technique. Wide variations in AR concentrations were found, but the following trends have been observed. The mean total cytosol concentration in untreated carcinoma is similar to that in benign hypertrophic (BPH) tissue, but the mean percentage of sites occupied by endogenous androgen was somewhat higher in BPH (85%) than in carcinoma (66%). Mean nuclear AR concentrations were also lower in carcinoma than in BPH, resulting in nuclear:cytosol ratios of 0.34 +/-0.25 for carcinoma and 0.78 +/-0.80 for BPH. Reduction of serum testosterone levels by orchiectomy and/or estrogen treatment resulted in a reduction of the mean nuclear: cytosol AR ratio to less than 0.2 in the carcinoma tissue, and to a reduction in the percentage of occupied cytosol sites. Mean total cellular AR in tissue from orchiectomized patients was lower than in untreated patients (249 fm/mg DNA vs 400 fm/mg DNA), but in estrogen-treated patients very high concentrations of total cellular AR were sometimes observed (up to greater than 4000 fm/mg DNA), due mainly to large amounts of free cytosol AR. This phenomenon is as yet unexplained. (no Refs)

38. NUCLEAR ANDROGEN RECEPTOR ASSAY IN BIOPSY-SIZE SPECIMENS OF HUMAN PROSTATIC TISSUE.

Blankenstein MA, Bolt-de Vries J, Foekens JA
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Prostate; 3(4):351-359 1982

The applicability of nuclear androgen receptors (NAR) assay to the biopsy-size specimens and the relationship between the presence of receptors and the response to endocrine therapy were studied in prostatic tissue samples from the patients with benign prostatic hyperplasia or prostatic cancer. Samples of 500, 100, 50, and 25 mg were homogenized, and the nuclear extracts were incubated with (3H)methyltrienolone. The NAR levels, on the av, did not depend upon the sample size. However, the intratissue variation coefficient increased when sample wt was less than 50 mg. The large variation in NAR levels observed in a 50-mg sample was associated with a nonhomogenous distribution of NAR over the prostatic tissue. The NAR levels did not depend upon the presence of molybdate in culture medium or upon the percentage of epithelium in the tissue. It was concluded that the assay can be used for prediction of the clinical response provided that multiple biopsies are analyzed. (14 Refs)

39. BIOCHEMICAL CHARACTERIZATION OF NORMAL PROSTATES AND PROSTATIC TUMORS DERIVED FROM NB RATS (MEETING ABSTRACT).

Chung LW, Thompson TC, Chao H
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Long-term administration of sex steroids (androgen or androgen plus estrogen) can induce prostatic adenocarcinoma in Nb rats (20-50% incidence). To explore the possibility of determining certain biochemical traits of the prostate that may accompany or precede the actual development of prostatic tumor histopathology, we investigated and established biochemical differences between ventral (VP), dorsolateral (DLP) prostates, and androgen-dependent (HDT) and independent (HIT) prostatic tumors derived from Nb rats. Both normal prostates and prostatic tumors contained high affinity cytosolic androgen receptor. Addition of sodium molybdate (10 mM) to the homogenizing medium enhanced (2-3 fold) the total cytosolic androgen receptor content in all tissues. Sodium molybdate, however, eluted a large quantity of androgen receptor from the crude nuclear pellet of HDT but not from HIT. Sucrose density gradient analysis revealed that the major androgen receptor species 'stabilized' by sodium molybdate in HDT sedimented at 8 S region. Analyses of enzyme activities in total tissue homogenates indicate similarities of arginase (AG), and leucine aminopeptidase (LAP) between HDT and DLP. Acid phosphatase (AP) and lactate dehydrogenase (LDH) were 60-80% higher in HDT than DLP. Most of these enzyme activities in HDT deviated markedly from that of the VP and HIT. Both HDT tumor lines (2Pr-128 and 2Pr-129) have remarkably similar enzyme activities. As compared to HDT, HIT contained similar AP but 7.3-, 5.2-, 2.3-, 4.0-and 0.37-fold LDH, alkaline phosphatase, LAP, beta-G and AG activities, respectively. (1 Ref)

STEROID HORMONE EFFECTS ON CELLULAR PROCESSES

40. IN VITRO AND IN VIVO EFFECTS OF DIETHYLSTILBESTROL AND ESTRAMUSTINE PHOSPHATE (ESTRACYT) ON THE MITOGEN RESPONSIVENESS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

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(c/o Kalland) Dept. Anatomy, Univ. Lund, Biskopsgatan 7, S-223 62 Lund, Sweden
Prostate; 3(4):405-414 1982

The effects of estrogen therapy on the immune system were studied in 20 patients (61-83 yr old) with confirmed diagnosis of prostatic adenocarcinoma and in 6 healthy young men. Seven patients with poorly differentiated carcinoma received estramustine phosphate (EMP: 840 mg/day, po, in three doses). Eight patients with Stage III-IV well or moderately differentiated carcinoma received diethylstilbestrol (DES: 10 mg/day, po, for 2 wk followed by 2 mg/day) in combination with polyestradiol phosphate (PEP: 80 mg, im, on day 1 of the treatment and then every fourth wk). Five patients with metastatic carcinoma received high doses of DES (1,000 mg/day x7, iv). Proliferative response of peripheral blood lymphocytes to concanavalin A (Con A) and to phytohemagglutinin (PHA) was studied before and during the treatment. In vitro incubation with EMP resulted in inhibition of Con A- and PHA-induced proliferation. DES was a less potent inhibitor of lymphocyte blast-transformation. Conventional treatment with EMP or with DES did not alter lymphocyte proliferation. High-dose DES therapy produced inhibition of PHA-stimulated lymphocyte proliferation. (39 Refs)

41. HYPERPROLACTINAEMIA IN MALES WITH AND WITHOUT PITUITARY MACROADENOMAS.

Spark RF, Wills CA, O'Reilly G, Ransil BJ, Bergland R
Steroid Res. Lab., Beth Israel Hosp., 330 Brookline Ave., Boston, MA, 02215
Lancet; 2(8290):129-132 1982

To ascertain whether in hyperprolactinemic men pituitary macroadenomas represent the end stage of a disease process wherein the only early symptom is impotence, the features of 16 hyperprolactinemic men with radiological evidence of pituitary macroadenomas were compared with those of 10 hyperprolactinemic men without pituitary macroadenomas. All were impotent and 25 had low serum testosterone levels. The group with pituitary macroadenoma was older (48.1 vs 63.2 yr) and had tolerated impotence for longer (10.4 +-6.0 vs 4.5 +-2.1 yr). Six of them had visual field defects (none in the other group), 14 had hypopituitarism (1 in the other group), and 14 were initially seen for problems other than sexual dysfunction (whereas all 10 without pituitary macroadenomas were seen primarily for evaluation of recent onset of impotence). In the macroadenoma group bromocriptine restored serum prolactin levels in 13 of the 16 and serum testosterone and potency in 5, whereas in the nontumor group it restored serum prolactin levels in all 10 and serum testosterone and potency in 9. (Author abstract) (19 Refs)

42. GONADOTROPIC ADENOMAS.

Warnet A, Lubetzki J, Gueris J, Franchimont P, Mikol J, Dubois M, George B
Service de Medecine interne, Hopital Lariboisiere, 2, rue Ambroise-Pare, F 75010 Paris, France
Ann Med Interne (Paris); 133(1):26-28 1982

Three patients with gonadotropic adenomas (GA) underwent hormone and immunofluorescent testing to establish a profile of clinical responses of patients with GA. Two patients were men (21 and 41 yr old) with intracrania! hypertension and bitemporal hemianopsia with optic atrophy. The third patient was a 61-yr-old woman with bitemporal hemianopsia with optic atrophy. In all three cases, the basal level of follicle stimulating hormone (FSH) was very elevated (21 to 50 nanog (ng)/ml compared with the normal value of 1.5 ng/ml). The response of FSH to multiple hormone stmulation was extremely high (2,550 and 1,350 ng/ml, normal 70 ng/ml) in the men, but the woman did not respond to this test. All patients demonstrated a prolonged response to luteinizing release hormone (CLRH). Luteinizing hormone was blocked in all three cases by the administration of testosterone or estradiol. Although the final diagnosis of the gonadotropic nature of an adenoma usually comes from in vitro studies, it is suggested that the existence of a large adenoma with pituitary deficits and hypersecretion of FSH is a decisive argument for a definite diagnosis. (19 Refs) (In FRE)

43. EFFECTS OF A PROLACTIN- AND ADRENOCORTICOTROPIN-SECRETING TUMOR ON GONADOTROPIN LEVELS AND ACCESSORY SEX ORGAN WEIGHTS IN ADULT MALE RATS: A POSSIBLE ROLE OF THE ADRENALS.

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Endocrinology; 111(2):412-417 1982

The presence of the transplantable PRL- and ACTH-secreting tumor 7315a in intact male rats resulted in very high serum PRL levels, decreased levels of LH and FSH, and reduced weights of testes and accessory sex organs. In gonadectomized rats bearing a small testosterone-filled capsule, the tumor inhibited the postcastration rise in gonadotropins and reduced the weights of the prostate and seminal vesicles. However, after adrenalectomy of intact or gonadectomized male rats bearing a small testosterone-filled capsule, inhibitory effects of the tumor on serum gonadotropin levels or on reproductive organ weights were totally absent. These results show that in adrenalectomized male rats, hyperprolactinemia in itself does not affect gonadotropin secretion and the androgenic action of testosterone. Rather, the tumor might exert a gonadotropin inhibitory action through elevated levels of PRL combined with progesterone, which is secreted by the ACTH-stimulated adrenal. (Author abstract) (27 Refs)

44. INFLUENCE OF HORMONAL STATUS INDUCED BY ESTROGEN-PROGESTERONE OVARIOSTATIC TREATMENT ON THE DIAGNOSTIC EFFECTIVENESS OF COLPOCYTOLOGICAL SCREENING FOR CARCINOMA OF THE UTERINE CERVIX.

Brizio PD, Armentano G, Tornatore GP
Divisione di Ostetricia e Ginecologia, Ospedale 'S. Maria di Misericordia', 17031 Albenga (Savona), Italy
Minerva Ginecol; 34(7/8):583-585 1982

Cervical smears showing signs of estrogen stimulation were found in 64/100 untreated women of child-bearing age without cytological lesions; such smears showed signs of progesterone stimulation in 36/100. Signs of progesterone and estrogen stimulation were found in 73/100 and 27/100 women, respectively, without cervical lesions under combined estrogen-progesterone treatment. Signs of progesterone and estrogen stimulation were found in 14/18 and 2/18 patients with cervical dysplasia during combined estrogen-progesterone treatment. (10 Refs) (In ITA)

45. EFFECTS OF ESTRADIOL ON ENZYMES ASSOCIATED WITH BENZO(A)PYRENE METABOLISM (MEETING ABSTRACT).

Williams MT
Department of Biochemistry, University of South Florida, College of Medicine, Tampa, FL, 33612
Fed Proc; 41(3):1428 1982

Injection of female C57Bl/65 mice with estradiol (E2) 24 hours prior to, during, and 24 hours after injection of 3-methylcholanthrene (3-MC) resulted in an apparent decrease in hepatic aryl hydrocarbon hydroxylase (AHH) activity when compared to AHH activity from animals receiving injection of 3-MC only. Moreover, AHH mediated binding of benzo(a)pyrene (BP) metabolites to DNA was inhibited between 35 and 45% in the 3-MC-E2 treated animals as compared to the 3-MC treated animals. The post-105,000 xg supernatant from E2 treated animals exhibitd significantly higher glutatione-S-transferase activity compared to supernatants from control animals. AHH activity in microsomes from control, E2 and 3-MC treated animals was significantly inhibited by BP quinones at a concentration as low as 2uM. AHH activity in microsomes from E2 treated animals was more sensitive to inhibiton by quinones than control AHH activity. Our data suggest that E2 may exert a direct inhibitory effect on hepatic AHH activity and also affect the activities of other enzymes associated with detoxification and inactivation of xenobiotics. (no Refs)

46. ENDOCERVICAL CHANGES IN THE GUINEA PIG AFTER TREATMENT WITH 17-BETA-ESTRADIOL AND 9,10-DIMETHYLBENZANTHRACENE.

Thomas JA, Dallenbach FD
Dept. Pathology, St. John's Medical Coll., Bangalore 560034, India
Indian J Med Res; 75:233-244 1982

Administration of 17-beta-estradiol simultaneously with 9,10-dimethylbenzanthracene to young female guinea pigs, produced marked endocervical mucosal hyperplasia. The hyperplasia showed basement membrane thickening, proliferation of basal cells, immature squamous differentiation with mild dysplasia, mucus cell differentiation and combined squamous and mucus cell differentiation. Excessive quantities of mucus were present in the well-differentiated mucus cell. This mucus appeared to be of two morphological types - the electron-dense and electron-lucent type with a fine fibrillar structure. Mucus was seldom seen to be released from these cells. When such release was seen, it was either by single-mucus-globule extrusion or by release of partial - or wholly - membrane bound mucus-globule-packets. The stroma also appeared stimulated. (Author abstract) (9 Refs)

47. HORMONAL REGULATION OF PROCARCINOGEN BIOTRANSFORMATION (MEETING ABSTRACT).

Rapic V, Kanazir D
Boris Kidric Institute of Nuclear Sciences, Belgrade, Yugoslavia
Twelfth Annual Meeting of the European Environmental Mutagen Society, June 20-24, 1982, Dipoli, Espoo, Finland. European Environmental Mutagen Society 250 pp., 1982.

It is known that the activity of hepatic drug metabolizing enzymes depend on the hormonal status of experimental animals. In this work the effect of adrenalectomy and hydrocortisone treatment on hepatic microsomal activity in biotransformation of B(a)P (benzo(a)pyrene) and 2-AAF (acetylaminofluorene) in the Ames assay were examined. Male Wistar rats aged 2 months were bilaterally adrenalectomized and ip treated with hydrocortisone at a daily dose of 25mg/kg, for 4 days after operation. S9 fractions were used in Salmonella typhimurium assays. Cytochrome P-450 and aminopyrine N-demethylase were determined in microsomal fractions. The results of the Ames test show that adrenalectomy significantly decreases enzyme activity of S9 fraction in metabolic transformation of 2-AAF and B(a)P. The hormone treatment restores the enzyme activity but not to the level of control. The results on aminopyrine N-demethylase activity are similar to S9 activity. Adrenalectomy also lowers the cytochrome P-450 content, but administration of hydrocortisone does not restore it viably. (no Refs)

STEROID HORMONE EFFECTS ON TUMOR GROWTH

48. HORMONAL RESPONSIVENESS OF THE HUMAN MALIGNANT MELANOMA CELL LINE HS0294 (MEETING ABSTRACT).

Lawson DH, Richmond A, Chawla PK, Nixon DW
Emory University School of Medicine, Atlanta, GA, 30322
Fed Proc; 41(3):736 1982

Both fibroblast growth factor (FGF, 50 ng/ml) and follicle stimulating hormone (FSH, 0.5 ug/ml) modestly enhance the incorporation of (3H)-thymidine into DNA in Hs0294 melanoma cels growing in serum-depleted medium. FSH treated cultures incorporated 39% more (3H)-thymidine than did controls and FGF treated cultures incorporated 18% more (3H)-thymidine than did controls. In contrast, insulin (5 ug/ml), transferrin (1 and 5 ug/ml), progesterone (2 x 10-8M), testosterone (2 x 10-8M), luteinizing hormone releasing factor (LRF, 1 ng/ml) epidermal growth factor (EGF, 5 and 15 ng/ml) and fetal calf serum (FCS, 0.75-200 ug of protein and 10%) did not stimulate (3H)-thymidine incorporation when added as single agents. When these same concentrations of insulin, transferrin, progesterone, LRF and FSH were added simultaneously, the hormonally treated cultures incorporated 100% more (3H)-thymidine into DNA than did control cultures. Elimination of FSH or any one of the other hormones in this combination decreased (3H)-thymidine incorporation only slightly. These results demonstrate that human melanoma cells exhibit a hormonal response similar to that reported for mouse melanoma cells. (no Refs)

49. CYCLOPHOSPHAMIDE PLASMA AND CEREBROSPINAL FLUID KINETICS WITH AND WITHOUT DIMETHYL SULFOXIDE.

Egorin MJ, Kaplan RS, Salcman M, Aisner J, Colvin M, Wiernik PH, Bachur NR
Lab. Clinical Biochemistry, Univ. Maryland Cancer Center, Howard Hall Tower, Room 9-024, 655 West Baltimore St., Baltimore, MD, 21201
Clin Pharmacol Ther; 32(1):122-128 1982

Ten patients with brain tumors and indwelling ventricular reservoirs were pretreated with 5% to 10% dimethyl sulfoxide (DMSO) (intravenous, oral, or both) and were then treated with 1.0 to 1.25 gm/m2 cyclophosphamide (CYC). All patients were also on anticonvulsants and dexamethasone. CYC and alkylating activity (alk act) in plasma and concomitant ventricular cerebrospinal fluid (CSF) were measured by gas chromatography and p-nitrobenzyl pyridine assay. CYC entered the CSF without difficulty and was lost from CSF more slowly than from plasma. Alk act did not enter CSF as well as did CYC. DMSO did not alter any measured aspect of CYC or alk act disposition. Specifically, it did not alter the CYC plasma half-life (t 1/2), CSF t 1/2, peak CSF:peak plasma CYC concentration ratio, or the urinary excretion of CYC. DMSO did not alter the plasma t 1/2 or urinary excretion of alk act or the peak CSF:peak plasma concentration ratio of alk act. Our data show reduced plasma t 1/2 of CYC and increased plasma and urinary alk act. This may reflect the effect of long-term therapy with anticonvulsants or steroids. (Author abstract) (46 Refs)

50. CHEMOTHERAPY AFTER OPENING BLOOD-BRAIN BARRIER: A NEW APPROACH TO TREATMENT OF MALIGNANT GLIOMAS (MEETING ABSTRACT).

Kori SH, Rekate HL, Bonstelle CT
No affiliation given
Neurology; 38(4,part2):A156 1982

Chemotherapy of gliomas may yield better results if the blood-brain barrier (BBB) is reversibly opened to chemotherapeutic agents by hyperosmolar carotid infusions. We treated six unequivocally terminal malignant glioma patients using this approach. All had massive recurrent tumor, as evidenced by CT (computer tomography) despite previous surgical resection and maximum doses of radiation, with or without chemotherapy. All patients had impaired consciousness despite large doses of steroids. On days 1 and 2, 100 mg/per square meter of BCNU (carmustine) was administered IV. On day 5, the BBB was opened by mannitol infusion into the appropriate carotid, followed by intracarotid infusion of Adriamycin (65 mg per square meter) and 5-FU (5-fluorouracil) (15 mg per kilogram). Opening of the BBB was confirmed by technetium scans. This treatment was repeated every 6 weeks. After a follow-up period of 2 to 12 months (mean, 5 months), five patients are alive. Only one patient, whose family decided to stop treatment, died. CT showed definite improvement in all cases. Three patients were able to walk and discontinue their steroids.

One patient, semiconscious at the beginning of therapy, is alive and functional at the end of 12 months. Despite the very advanced stage of disease in all of our patients, these results are encouraging and open a new avenue for the treatment of malignant gliomas. (no Refs)

51. PH1 POSITIVE ACUTE LYMPHOBLASTIC LEUKAEMIA: EXPERIENCE OF MENINGEAL RELAPSE IN THREE CASES (MEETING ABSTRACT).

Smith AG, Lucie NP, Dagg JH, Prentice AG, Helenglass G, Browning JD

Departments of Hematology and Medicine, Western Infirmary, Glasgow, Scotland

Br J Haematol; 50(4):695 1982

Conflicting opinions arise as to the optimal management of Ph1 positive acute lymphoblastic leukemia (ALL) although it is clear that reasonable remissions can be obtained using vincristine and corticosteroids. We have recently treated three cases of this disease using an induction regime of vincristine, adriamycin, cyclophosphamide and prednisolone and maintenance therapy based on 6-mercaptopurine and methotrexate. All achieved a complete remission of ALL. During remission peripheral blood and marrow mitoses continued to show the presence of the Ph1 chromosome. In each case ALL remission was terminated at 6, 15 and 17 months respectively by meningeal relapse. The first case did not receive any form of CNS prophylaxis. The remaining two cases received prophylaxis with intrathecal methotrexate alone in one and additional cranial irradiation (2400 rads) in the other. Comparatively long survival was achieved in all cases from the diagnosis of ALL (12, 34 and 20 months). While these numbers are very small the differences between the first case and the other two in duration of first remission and overall survival are striking. Our experience suggests that the onset of the unpleasant complication of meningeal leukemia in this disease may be delayed by CNS prophylaxis. In Ph1 positive ALL we would welcome the results of a large scale trial of this modality therapy. (no Refs)

52. INFLUENCE OF PREGNANCIES ON PROLACTINOMAS.

Rjosk HK, Fahlbusch R, Von Werder K

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Acta Endocrinol (Copenh); 100(3):337-346 1982

Hyperprolactinemic patients desiring pregnancy with a normal sella turcica or radiological evidence for a microprolactinoma without suprasellar extension were treated with bromocriptine. Females desiring pregnancy with large adenomas or suprasellar extension were treated by transsphenoidal surgery and in most instances post-operatively with bromocriptine. This differentiated management allowed the outcome of 65 pregnancies with delivery at term without complications related to the sella turcica. Considerable variations of prolactin levels during pregnancy suggesting different estrogen sensitivity of the prolactinoma cells were encountered. However, a rapid fall of the prolactin levels in 60 patients after termination of pregnancy indicated that estrogen stimulation does not cause persisting growth of the adenoma. In contrast, in 10% of pregnancies of hyperprolactinemic patients a reduction of the prolactin levels has been observed leading to spontaneous ovulatory cycles in five patients. (Author abstract) (22 Refs)

53. A COMPARISON OF TWO CYTOTOXIC REGIMENS IN ADVANCED BREAST CANCER (MEETING ABSTRACT).

Blake JR, Blamey RW, Wilson RG, Benton FM

University Department of Surgery, The City Hospital, Nottingham, England

Clin Oncol; 8(1):83 1982

A consecutive number of 102 women with advanced breast cancer has been treated with two cytotoxic regimens CMFVP (Cyclophosphamide, Methotrexate, 5-Fluorouracil, Vincristine and Prednisolone) (n equals 84) and with Melphalan and Methotrexate (n equals 18). Treatment has been on an outpatient basis for 6 months or longer, and response has been according to UICC criteria with the definition that a response should be maintained for at least 6 months. The two groups are comparable for age, site of disease and for time interval from diagnosis. The overall response has been 28.4%, the response for CMFVP (33.3%) being significantly better than for Melphalan and Methotrexate (56%). Two factors which show a likelihood of a response to treatment are age and estrogen receptor (ER) status of the primary tumor. Remission following cessation of therapy has been short-lived, (the estimated median survival from start of therapy for responders 20 months and for nonresponders 9 months). However, a comparison of survival from time of diagnosis shows no significant difference between the two groups. Cytotoxic therapy is a palliative benefit to some patients, but we feel that a more accurate identification of patients likely to respond to treatment is needed. (no Refs)

54. SHORT-TERM CULTURE OF HUMAN BREAST CANCER: IN VITRO EFFECTS OF HORMONES RELATED TO PATIENT RESPONSE.

Poulsen HS, Bichel P, Andersen J

Inst. Cancer Res., Radiumstationen, 44 Norrebrogade, DK-8000 Arahus C, Denmark

Br J Cancer; 46(1):67-74 1982

Breast-cancer tissue from 60 patients was tested for estrogen and testosterone sensitivity in vitro by measuring [3H]-dT incorporation in tissue fragments at various times during 48 hr culture. Hormone sensitivity in test culture was determined as an increase or decrease in dT uptake. In vitro cultures of breast-cancer tissue demonstrate that some tumors are hormone-sensitive and others hormone-insensitive, but it cannot be predicted whether cell proliferation is stimulated or inhibited by hormone treatment. The data were related to the clinical stage of the patients, menopausal status, and the degree of anaplasia of the tumors tested. No correlation was observed between these parameters and in vitro hormonal sensitivity. However, when related to the response of patients to various kinds of hormonal treatment, a significant positive correlation was obtained. (Author abstract) (22 Refs)

55. BREAST CANCER AND ESTROGEN REPLACEMENT THERAPY.

Hulka BS, Chambless LE, Deubner DC, Wilkinson WE

Dept. Epidemiology, Univ. North Carolina, Rosenau Hall 201 H, Chapel Hill, NC, 27514

Am J Obstet Gynecol; 143(6):638-644 1982

Concern over the possible effect of estrogen replacement therapy on the subsequent development of breast cancer prompted us to compare 199 postmenopausal breast cancer patients with 451 hospital control subjects and 852 community control subjects on their prior use of estrogens. Estrogen use did not increase the breast cancer risk for women with a surgical menopause. Among women with a natural menopause, estrogens administered by all routes were associated with breast cancer risks of 1.7 or 1.8. There was no coherent pattern of changing risks with varying durations of use, different daily dosages, years since first use of estrogen, or years since most recent use. When women who usually received estrogen by injection were excluded, the risk estimates for oral estrogens were 1.3 (case subjects compared to community control subjects) and 1.2 (case subjects compared to hospital control subjects). These increases were not statistically significant. Use of injectable estrogens produced a four-fold increase in breast cancer risk among naturally postmenopausal women. (Author abstract) (14 Refs)

56. THERAPY OF BREAST CANCER.

Rodriguez Garcia JR, Cayuela Leclert J, Revert JJ, Sanchez R, Bolea T, Navarrete Montoya A
Departamento de Obstetricia y Ginecologia, Ciudad Sanitaria 'Virgen de la Arrixaca', Murcia, Spain
Toko Ginecol Pract; 41(468):79-88 1982

Breast cancer was diagnosed in 116 women during the period 1975-1980. Infiltrating ductal cancer was found in 98 cases, lobulated cancer in 9, Paget's disease in 3, medullar carcinoma in 3, adenoid cystic carcinoma in 1, tubular carcinoma in 1, and skin cancer in 1. Two patients were in Stage 0, 18 in I, 67 in II, 20 in III, and 9 in IV. The patients in Stages I and II, as well as the Stage III patients with tumors smaller than 6 cm were subjected to preventive chemotherapy, and those without estrogen receptor activity to antiestrogen hormone therapy. The Stage III patients with tumors larger than 6 cm were subjected to preoperative radiotherapy. The mortality rate, determined for 95 treated patients, was 3/67 (median survival time 4 yr) in Stage II and 5/20 (median survival time 2.4 yr) in Stage III. The mortality rate was 0% for the patients without lymph node metastases, 8.82% for those with 1-4 lymph node metastases and 13.36% for those with more than 4 lymph node metastases. The 5-yr survival rates were 100% in Stage I, 77% in II and 50% in III. (13 Refs) (In SPA)

57. ESTROGEN REPLACEMENT: ITS BENEFITS AND ITS RISKS.

Skillman TG
Ohio State Univ. Coll. Medicine, Columbus, OH
Consultant; 22(7):115,116,119,125,127 1982

Benefits and risks of estrogen replacement therapy (ERT) are evaluated. ERT counteracts the effects of estrogen depletion. Specific indications for ERT include vasomotor hyperactivity, depression, gynecologic problems, and osteoporosis. Risks of ERT include a higher rate of endometrial cancer, unmasking of hypertension, generation of lithogenic bile, modification of lipoproteins, and disturbances of the clotting mechanism. ERT apparently does not increase the risk of breast cancer. A determination for or against use of ERT depends on evaluation of factors in each case. (7 Refs)

58. INCREASED ANDROGENIC ACTIVITY IN WELL-DIFFERENTIATED ENDOMETRIAL ADENOCARCINOMA.

Grattarola R
Ottava Strada 32, 20090 Milano Sifelice, Italy
Gynecol Oncol; 14(1):40-48 1982

Well-differentiated adenocarcinoma of the endometrium was diagnosed in three patients with polycystic ovary syndrome (PCO) and in two long-term users of an oral contraceptive (ethinylestradiol plus dimethisterone), all five at premenopausal age (from 28 to 36 yr). These patients had high urinary testosterone. None underwent hysterectomy; the three with PCO were treated by wedge resection of the ovaries, and the two oral contraceptive users by simple curettage and discontinuation of oral contraception. The treatment was able to revert the endometrial pattern to normal as well as decrease the urinary level of testosterone. These patients were followed up for 3 to 10 yr since the hormonal study and none has so far had a recurrence. The testosterone excretion level was determined in an additional 26 patients with well-differentiated adenocarcinoma and in 14 with undifferentiated adenocarcinoma of the endometrium. It was found that the testosterone excretion level was significantly increased in patients with well-differentiated adenocarcinoma but not in patients with undifferentiated adenocarcinoma of the endometrium. (Author abstract) (18 Refs)

59. PROGESTOGEN THERAPY FOR OVARIAN CARCINOMA.

Timothy I
Dept. Obstetrics and Gynaecology, Leighton Hosp., Crewe, Cheshire, England
Br J Obstet Gynaecol; 89(7):561-563 1982

Treatment of 15 women (31-75 yr old) with ovarian carcinoma with a new progestogen, gestronol hexanoate (GHX), is reported. Most patients received one injection of 200 mg GHX/wk; when tumor size increased or when the patient felt unwell, the dose was increased to 400 mg 1x/wk or 200 mg 2x/wk. While duration of survival was not increased, the quality of life was improved by a sense of well-being despite advanced disease. Many of the patients remained well, gained wt, and had no sign of recurrence for periods up to 72 mo. GHX was administered immediately after surgery or up to 1 wk after diagnosis. Most of these patients had been treated previously with alkylating agents after surgery; however, side effects outweighed the improvements noticed. Nine of the patients were alive with no recurrence of growth for 6-72 mo from the first dose of GHX. Five patients experienced recurrence 9-24 mo after the first GHX dose. One patient exhibited a decrease in tumor size allowing easy excision. Use of GHX is recommended for improving the quality of life of patients with ovarian carcinoma. (3 Refs)

60. TAMOXIFEN, AMINOGLUTETHIMIDE AND DANAZOL: EFFECT OF THERAPY ON HORMONES IN POST-MENOPAUSAL PATIENTS WITH BREAST CANCER.

Coombes RC, Powles TJ, Rees LH, Ratcliffe WA, Nash AG, Henk M, Ford HT, Gazet JC, Neville AM
Ludwig Inst. Cancer Res. (London Branch), Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Br J Cancer; 46(1):30-34 1982

Gonadotrophins, estradiol, androstenedione, testosterone and dehydroepiandrosterone sulfate (DHAS) were measured sequentially in 72 patients with advanced breast cancer receiving endocrine therapy of various types. Tamoxifen significantly reduced gonadotrophins but did not effect other hormones. Danazol also reduced gonadotrophins. Aminoglutethimide (AGT) reduced estradiol and DHAS but had no effect on gonadotrophins. The effects of administering tamoxifen, AGT and danazol together (TAD) were therefore examined. This combination reduced gonadotrophins, estradiol and DHAS, but no further than tamoxifen and AGT alone. The degree and duration of hormone suppression were similar in both responders and non-responders to tamoxifen, AGT or TAD, though patients responding to AGT showed more complete suppression at the end of the course of treatment, perhaps because they were treated longer. On relapse, adequate gonadotrophin and steroid suppression was demonstrated in patients receiving tamoxifen and AGT, respectively. We conclude that (a) response to endocrine therapy is unlikely to be related to the degree of endocrine suppression produced by the therapy; (b) combination endocrine therapy does not further reduce serum-hormone concentrations and (c) relapse is unlikely to be due to escape from the hormone-inhibitory effects of endocrine agents. (Author abstract) (11 Refs)

61. ENDOCRINE PROBLEMS IN THE MENOPAUSE.

Hammond CB, Ory SJ
Duke Univ. Medical Center, Durham, NC
Clin Obstet Gynecol; 25(1):19-38 1982

The climacteric is an interval characterized by a multitude of physiologic, psychologic, and sociologic alterations that result in an individual's adaptation to life beyond reproduction. The common denominator of the physiologic changes is the loss of functional ovarian follicles and their ability to produce estradiol. The relative estrogen deficiency results in a myriad of systemic changes, some of which in themselves may impair the quality of life or be life-threatening. Estrogen replacement therapy is effective in alleviating some of these changes, including osteoporosis, vasomotor symptoms, and genital atrophy. This treatment, however, confers additional risks, endometrial adenocarcinoma being the one of greatest concern. This risk can be reduced by carefully selecting patients to be treated, closely following them, minimizing the duration and amount of exposure, and adding a progestin to the regimen. It is hoped that the risk of endometrial cancer and other adverse reactions associated with estrogen use can be further reduced when more data regarding optimum dosage and choice of agents are available. (Author abstract) (119 Refs)

62. SILENT HEPATIC LESIONS DETECTED WITH COMPUTED TOMOGRAPHY IN APLASTIC ANEMIA PATIENTS ADMINISTERED ANDROGENS FOR A LONG PERIOD.

Yamagishi M, Hiraoka A, Uchino H
Health Care Center, Shiga Univ., Shiga, Japan
Nippon Ketsueki Gakkai Zasshi; 45(4):703-710 1982

Macroscopic liver lesions were investigated with the use of computed tomography (CT) and radionuclide imaging (RN) in 15 aplastic anemia patients who were administered anabolic steroids for over 1 yr and who showed no apparent physical and biochemical sign of liver tumor. In three patients, CT scans showed radiolucent areas in the liver. Contrast enhancements revealed these lesions to be well vascularized, suggesting they were not cysts but probably tumors. RN imaging could not demonstrate any definite space occupying lesions. Total dose of AS administered to each of the three patients exceeded 30,000 mg. It was felt that attention should be paid to the possible development of hepatic tumor when the dose of AS administered exceeds 30,000 mg. (Author abstract) (9 Refs)

63. AMINOGLUTETHIMIDE IN OESTROGEN ESCAPED PROSTATIC CANCER (MEETING ABSTRACT).

Stone AR, Rees WM
Cardiff Royal Infirmary, Cardiff, Wales
Br J Urol; 54(1):74 1982

In prostatic cancer the duration of responsiveness to either oral estrogens or orchiectomy is variable. A large proportion of patients eventually become resistant to this conventional form of androgen suppression and show progression of tumor at this time. Treatment of this 'estrogen escaped' prostatic cancer is usually palliative and often ineffective. In this study the response of a group of patients with advanced prostatic cancer to further androgen suppression with aminoglutethimide has been assessed. The patients were given aminoglutethimide 250 mg qds and hydrocortisone 20 mg bd. During this therapy the subjective response has been monitored using several subjective parameters. The objective response to therapy has been measured by serial bone scanning and acid phosphatase estimations, both by enzymatic and immunoassay methods. The endocrine effects of the drug have been monitored by serial hormone profiles. The serum levels of the drug, its side effects and patient tolerance have been recorded. Four of the 10 patients followed up had a significant relief of symptoms, but the subjective response was of short duration. There was no evidence of objective regression of the disease drug treatment. The study is continuing but results have been disappointing. (no Refs)

64. PROGNOSIS OF PROSTATE CANCER.

Rannikko S
Second Surgical Unit, Helsinki Univ. Central Hosp., Helsinki, Finland
Duodecim; 98(4):258-266 1982

A total of 176 prostate cancer cases were diagnosed and treated in 1967-1971 in the Urology Department of the Second Surgical Unit, of the Helsinki University Central Hospital. The patients were divided into two age groups: under 70 yr old (89 patients) and 70 yr old or more (87 patients). The TNM classification and differentiation categories of UICC were used for the study. Ninety percent of the patients were treated with orchiectomy, estrogen therapy (polyestradiol phosphate) or a combination of these. Five-year survival was experienced by 41%-50% of the patients with metastasis at the time of diagnosis, and 25% of the others. The more poorly the tumors were differentiated, the more extensive the spread of the disease, and the less chance of five-year survival. If the primary tumor had penetrated to the exterior of the capsule, the metastasis was not a factor in the prognosis. Conversely, local spread of the malignancy did not significantly affect prognosis if metastasis had already occurred. In the younger group of patients the figure for spread, differentiation and five-year survival differed significantly from that of the older group. There were no difference in prognosis between those who were treated with surgery alone and those who were treated only with estrogens. The estrogen administered in doses of 80-160 mg per month im, did not increase mortality due to cardiovascular disease. Mortality due to other primary malignancies was not greater than expected. Prostate cancer was the third most common form of cancer in Finland in 1979, with 700 new cases occurring annually. (48 Refs) (In FIN)

65. INDUCTION OF A NEW CLASS OF ESTROGEN-DEPENDENT MESENCHYMAL TUMORS IN RABBITS (MEETING ABSTRACT).

Galt RM, Coogan PS, Laing GH, Newton JJ, Hass GM
Rush University, Chicago, IL, 60612
Fed Proc; 41(3):330 1982

One hundred and fifty-six young virgin female (F) and male (M) albino rabbits, divided into groups, were placed on regimens, permuting the following urogenital tumorigenic factors: 240 mg% dietary 2-AAF (2-acetylaminofluorene); gonadectomy (G); 25 mg pellet sc of 17 beta estradiol (Progynon) (E2);

25 or 50 mg im weekly of medroxyprogesterone (Depo-Provera) (P). Pathologic studies showed frequently unique benign multicentric neoplasms of the spleen, kidneys and liver with occasional malignant transformation of those in the spleen. Though there was no proof of common histogenesis, all were composed of large clear pleomorphic undifferentiated mesenchymal cells, productive of a loose glycoprotein-rich intercellular matrix. Tumors occurred at random in spleen and liver but only distally in medullary renal pyramids. Induction required E2 though malignant transformation also required 2-AF, two factors favorable for induction of urogenital tumors. However, occurrence of urogenital tumors was eliminated by the best regimens for induction of the extra-urogenital neoplasms; namely, combinations of 2-AAF, E2 and P. For example, among 16 F and 10 M on these regimens for 21-69 weeks, 20 had splenic tumors of which 7 were malignant, 6 had renal tumors and 2 had liver tumors. Therefore, progesterone was the principal mediator of high incidence of these unique estrogen-dependent mesenchymal tumors in spleen, liver and kidneys of rabbits. (no Refs)

66. PRELIMINARY STUDY ON THE ROLE OF CO-FACTORS IN INDUCING CERVICAL CANCER IN MICE BY GENITAL HERPES SIMPLEX VIRUS.

Chen MH, Swen Y
Dept. Cell Biology, Inst. Virology, Hupeh Medical Coll., Wuhan City, People's Republic of China
Excerpta Med Int Congr Ser; 571:351-357 1982

The possible interactions of various factors such as genital herpes simplex virus (HSV), lymphatic leukemic virus (LLV), HSV and local trauma (LT), and HSV and cortisone, in the development of cervical cancer were studied in 2-mo-old random bred female mice. LT was produced by stroking a brush against the cervix. One group of mice received ip cortisone (0.3 mg, 1x/wk) for 3 wk before inoculation with HSV. The study involved the use of 50 controls and 285 surviving mice in six treatment groups. Mice which survived over 1 yr were killed. The entire reproductive tract was studied by permanent histologic preparations. No precancer or cancer was noted in groups treated with HSV (50 mice) or LLV (21 mice) alone. One precancer was noted among 63 mice subjected only to LT. Precancers and cancers were noted, respectively, as follows: in 6 and 3 in 41 mice with HSV + LLV; in 8 and 3 in 68 mice with HSV + LT; and in 6 and 2 in 51 mice with HSV + cortisone. The cancers found included squamous cell carcinoma of the vagina, adenoid carcinoma found both in the cervix and vagina, adenoid carcinomas of the cervix and vaginal fornix, and squamous cell carcinoma in the vaginal fornix. The data suggest possible interaction of HSV and LLV, HSV and LT, and HSV and cortisone in the development of cervical cancer in mice. (15 Refs)

67. HORMONES AND MEDICATIONS (MEETING ABSTRACT).

Lipsett MB
National Institutes of Health, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A7 1982

Hormones have been shown experimentally to act as cocarcinogens or promoters, ie, they facilitate the carcinogenic event. In the cases of breast and endometrium, those hormones that facilitate growth may also favor carcinogenesis in the human. There is good epidemiologic evidence of breast and endometrial cancer, the risk increasing with increasing duration of use. Periodic progestin-induced withdrawal will probably mitigate the risk of endometrial cancer after the menopause. Prolactin is the important promoter of mammary cancer in the rat and mouse, but its significance in women is still under study. Intermittently elevated prolactin levels have been noted in some women who subsequently developed breast cancer, but epidemologic studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk. Diethylstilbestrol is listed as a carcinogen but any estrogen can induce mammary cancer in the rodent or vaginal adenosis in the neonatal mouse (an experimental model of human vaginal adenocarcinoma). (no Refs)

68. HORMONE DEPENDENCY IN N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS.

Arafah BM, Finegan HM, Roe J, Manni A, Pearson OH
Dept. Medicine, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Endocrinology; 111(2):584-588 1982

The majority (87%) of N-nitrosomethylurea-induced rat mammary tumors regressed within 1 wk after hypophysectomy (hypox). After a hypox-induced tumor regression, ovine PRL (oPRL), and 17beta-estradiol (E2) were administered separately or in combination in order to define the individual role of these hormones in regulating tumor growth and influencing estrogen (E), progesterone (Pg), and PRL receptor (R) levels. Administration of E2 (2.5 ug twice daily) or oPRL (20 IU daily, started 5 days after hypox and continued for 10 days), resulted in stabilization of tumor growth. Simultaneous administration of E2 and oPRL resulted in a synergistic effect and reactivation of tumor growth. ER levels in mammary tumors were significantly lower than those in the control 15 days after hypox (p less than 0.01). Treatment with E2, oPRL, or both simultaneously had no significant effect on ER levels. A significant decline in PgR levels was noted at both 5 and 15 days after hypox. Whereas treatment with oPRL had no significant effect on PgR levels, E2 administration either alone or in combination with oPRL restored PgR levels to control values. PRLR levels were unchanged from control values at 5 days, but significantly declined (p less than 0.005) 15 days after hypox. Treatment with E2, oPRL, or both hormones simultaneously partially maintained PRLR and prevented the decline to the extremely low level noted in the untreated group. We conclude that the growth of nitrosomethylurea-induced rat mammary tumors is dependent on both E2 and PRL. There was a synergistic effect between E2 and PRL on tumor growth but not on ER, PgR, or PRLR. Neither E2 nor PRL had any significant effect on ER after hypox. PgR is under E2 control. Either E2 or PRL or both hormones were able to maintain PRLR in mammary tumors after hypox. (Author abstract) (17 Refs)

69. EFFECT OF SEX HORMONES ON THE EXPERIMENTAL INDUCTION OF CANCER IN RAT STOMACH - A PRELIMINARY STUDY.

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Digestion; 23(3):151-155 1982

The effects of sex hormones on the induction of gastric carcinoma by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were investigated in Wistar rats. Well-differentiated adenocarcinomas developed with high frequency (88%) on the glandular stomach of male rats given MNNG in drinking water (50 ug/ml) for 4 mo and sacrificed on the 12th mo of the experiment. In female rats given MNNG, no gastric cancer was observed. In the castrated or estradiol-treated male rats, the incidence of carcinoma was lower (29 and 68%, respectively) than in the nontreated male rats. Histologically, poorly differentiated adenocarcinomas were observed more frequently in these groups than in the nontreated male group. In MNNG carcinogenesis, female, castrated male and estrogen-treated male rats had a lower incidence of gastric cancer with lower histological differentiation than did nontreated male rats. (Author abstract) (11 Refs)

70. LACK OF HEPATOGENOTOXICITY OF ORAL CONTRACEPTIVE STEROIDS.

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Carcinogenesis; 3(6):625-628 1982

The objective of the present study was to determine whether mestranol could initiate hepatocarcinogenesis and whether various gonadal steroids have detectable hepatogenotoxic potential. To test for initiation potential, female, Sprague-Dawley rats were partially hepatectomized and intubated with mestranol (100 or 500 mg/kg) 24 hr later. Twenty-four hr after treatment all rats were transferred to diet containing 0.05% phenobarbital to promote hepatocytes initiated by mestranol treatment. Four mo later an analysis of putative preneoplastic gamma glutamyl transpeptidase positive foci indicated that mestranol did not cause a significant increase in the number of such foci. Hepatogenotoxicity was assessed in two ways, first using alkaline elution to detect liver DNA damage after in vivo treatment with mestranol, and second by detection of DNA repair synthesis in primary cultures of hepatocytes treated with various oral contraceptive steroids. The results of both studies were negative. In conclusion, the oral contraceptive steroids do not exhibit strong initiating or genotoxic potential. (Author abstract) (21 Refs)

71. GROWTH REGULATION AND TUMOR PROMOTION BY STEROID HORMONES IN THE RAT LIVER.

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Onkologie; 4(3):120-124,127-132,135-136 1981

Corticosterone both inhibits cell proliferation in the liver of adult rats and synchronizes division of liver cells after partial hepatectomy. By adrenalectomy, corticosterone can be eliminated from the circulation at least for certain time. Additionally it can be inactivated in the liver cell by competitive inhibition of its cytoplasmatic receptor. Both these procedures lead to an increased cellular proliferation. The influence of these processes on the development of chemically induced liver tumors has been investigated. Animals died significantly earlier from hepatomas, when they had been treated with both diethylnitrosamine and steroids belonging to the group of gestagens, androgens and estrogens (which stimulate proliferation). Therefore, a tumor-promoting effect of these substances can be assumed. (Author abstract) (146 Refs) (In GER)

72. SPONTANEOUS OCCURRENCE OF ATYPICAL HYPERPLASIA AND ADENOCARCINOMA OF THE UTERUS IN ANDROGEN-STERILIZED SD RATS.

Morikawa S, Sekiya S, Naitoh M, Iwasawa H, Takeda B, Takamizawa H

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JNCI; 69(1):95-101 1982

In SD female rats sterilized by a single injection of testosterone propionate at 2 days after birth, the spontaneous occurrence of atypical hyperplasia and adenocarcinoma of the uterus was observed for a fairly long period (greater than 2 yr). Two atypical hyperplasias and two adenocarcinomas were detected in 25 androgen-sterilized rats (ASR) after 500 days of age; in contrast, in 111 normal control rats no abnormal uterine proliferation was detected during a 750-day observation period. These results indicate that a persistence of both hormone imbalances and dysfunctional uteri in ASR induces abnormal uterine proliferation at a late age. (Author abstract) (31 Refs)

GENERAL REVIEWS ON STEROID HORMONES

73. THE APPLICATION OF STEROID RECEPTOR ASSAY IN HUMAN PROSTATE CANCER RESEARCH AND CLINICAL MANAGEMENT (REVIEW).

Ekman P

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Anticancer Res; 2(3):163-171 1982

Principles, methods, uses, and results of steroid receptor assays in research on human prostatic cancer are reviewed. The mechanisms by which steroid hormones affect prostate cells are evidently similar to mechanisms in other target organs. The presence of hormone receptors is apparently required for sensitivity to hormones. The prostate gland is a target organ of androgens. Tumors of the prostate are heterogeneous; tumors are probably not entirely receptor-positive or receptor negative, but rather contain cells with varying numbers of receptors. Most research has been done with rats or dogs. No animal model has been found suitable for studies of human prostatic cancer, however. Obtaining adequate samples of human tissue is difficult. Receptor studies are complicated by problems with receptor stability, cross-reactivity, and the difficulty of making quantitative measurements. Reproducible studies have produced values for the amounts and dissociation constants of androgen, estrogen, progestin, and estrogen receptors in benign prostatic hyperplasia. Values for prostatic cancers are more variable than those for benign tumors. Various forms of hormone therapy have been effective to varying degrees in control of benign hyperplasias and prostatic cancers. The success of therapy has been related to the levels of steroid receptors in the tumors. (112 Refs)

74. EPIDEMIOLOGY OF BREAST CANCER.

Marchant DJ

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Clin Obstet Gynecol; 25(2):387-392 1982

The incidence of breast cancer (BC) and risks associated with BC are discussed. A number of factors have been associated with increased risk for BC including demographic, anthropometric, dietary, menstrual, reproductive, hormonal, genetic, and others, including a history of benign breast disease. Key risk factors include previous cancer of one breast, age, age at menarche, age at full-term pregnancy, age at menopause, and wt. The woman with previous cancer of one breast is at risk for cancer in the opposite breast. Studies indicate that the risk is approx 1% per yr. Evidence suggesting that estrogens play an important part in determining the hormonal milieu that favors the development of human BC exists. Risk factors noted in epidemiologic studies are associated with changes in the production of estrogen. Height and wt factors that contribute to increased risk in postmenopausal women can be explained by increased peripheral conversion of androgen to estrogen. The administration of estrogens to postmenopausal women may result in a small increase in the risk of BC. Growth rate of human malignant BC cells in tissue culture is enhanced by estrogens in physiologic concentration. Therapeutic strategies that are effective in the treatment of BC in premenopausal women can be explained on the basis of reduction or elimination of endogenous estrogens. Recent studies on the mechanism of action of estriol indicate that it is neither an impeded estrogen nor an estrogen antagonist when present in continuous of chronic fashion. Most investigators suggest that estrogen is preparative rather than carcinogenic. One of the risk factors that is alterable is obesity, particularly in the postmenopausal woman. (14 Refs)

75. PRIMARY TREATMENT OF BREAST CANCER.

Nichols DH
Brown Univ., Providence, RI
Clin Obstet Gynecol; 25(2):425-431 1982

A broad outline is presented of the treatment of breast cancer which includes preoperative evaluation, preoperative and postoperative staging, and modalities of treatment (surgery, endocrine and radiation therapy, and adjuvant chemotherapy). It is concluded that modified radical mastectomy is the treatment of choice for most invasive carcinomas, except in patients with deeply situated tumors lying adjacent to the pectoral fascia in whom Halsted radical mastectomy may be indicated. In patients with positive axillary metastases, adjuvant chemotherapy should be considered starting in the immediate postoperative phase and continued at full dosage for at least 9-12 mo. Endocrine manipulation by oophorectomy in patients with estrogen-receptor-positive tumors should be considered in those who relapse following chemotherapy. Routine postoperative radiation therapy is not recommended. While not proven at the present time, the use of adjuvant chemotherapy in all patients regardless of nodal status may be considered because of the projected long-term survival. (20 Refs)

76. THE MEDICAL MANAGEMENT OF BREAST CANCER.

Costanza ME
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Clin Obstet Gynecol; 25(2):433-441 1982

With regard to breast cancer, discussions are centered around the use of adjuvant chemotherapy, determination of recurrence, the value of estrogen receptor (ER) assay, and evaluation of the extent of disease and menopausal status. Principles of treatment are discussed in relation to menopausal status, ER activity, organs involved, varying temporal aggressiveness of tumors, and response measurement. Treatment is also discussed in the presence of single metastases, and where estrogen status is unknown. Various procedures for hormonal manipulation are outlined. The use of tamoxifen as an antiestrogen and aminoglutethimide for suppression of corticosteroids is discussed as is hormonal response in relation to site of metastasis, the interval between diagnosis and recurrence, sequence of therapy, and use of hormones plus chemotherapy. The most important recent advance in the treatment of advanced breast cancer is the concept of combination chemotherapy. Two strategies are presented for treatment of recurrent disease in premenopausal and postmenopausal ER-positive patients. Outside of results in protocol studies, most treatment has a 'palliative' cast, although long survival sometimes occurs. Since cure is not regularly achieved in metastatic disease, superintensive programs generally are inappropriate. There should be a balance between length of survival and the quality of that survival. (no Refs)

77. CHEMOTHERAPEUTIC TREATMENT OF ENDOMETRIAL CARCINOMA.

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Clin Obstet Gynecol; 25(1):93-99 1982

The available data on the use of hormonal and nonhormonal chemotherapy in the treatment of patients with endometrial cancer (EC) are summarized. Analysis of reports of treatment of advanced or recurrent EC with progestins showed an objective response with 17-alpha-hydroxyprogesterone caproate in 32% of patients. Discovery of steroid receptors might help to explain the therapeutic action of progestational agents in advanced EC. Hormonal effects are mediated by complexes formed by interaction of the steroid and its receptors. Tumors that lack receptors are unresponsive to the hormone. Thus, patients with EC devoid of progesterone receptors will not respond to progestin therapy. An objective response to tamoxifen of 30% was observed in 10 patients. The role of nonhormonal therapy in the management of EC has been restricted because of the previously demonstrated response of this tumor to surgery, radiotherapy, and progestins. Chemotherapy is employed most often for recurrent or advanced tumors beyond the control of surgery and irradiation. Single agents in treatment of EC are 5-fluorouracil (5-FU), cyclophosphamide (CY), adriamycin (ADM), and cis-platinum. Only two controlled prospective trials have evaluated the efficacy of combination chemotherapy regimens in patients with advanced and recurrent EC. One compared the efficacy of melphalan, 5-FU, and megestrol acetate (MEA) with CY, ADM, 5-FU, and MEA; and the other CY, ADM, and MEA with CY, 5-FU, and MEA. The overall objective response rate of combination chemotherapy regimens was not higher than the objective response rate for single-agent therapy with ADM. (40 Refs)

78. DES.

Minor LS
West Jefferson Medical Group, Los Angeles, CA
Hosp Physician: 18(7):66-68,70-71 1982

The history of the diethylstilbestrol (DES) hazard, biological effects of DES, the population at risk, and counseling of persons at risk are discussed. DES was prescribed between 1941 and 1971 to prevent miscarriages. The drug was withdrawn from use for this purpose when adverse health effects were found. DES is a synthetic estrogen that acts primarily on the Mullerian system in the fetus. DES inhibits the normal replacement of Mullerian tissue by urogenital epithelium as the fetus develops. Women who received DES and children who were exposed to DES in utero may show adverse effects of DES. In males exposure to DES may result developmental anomalies in the urogenital system. No cancers in males have been linked to

DES. In daughter of women who received DES, the effects of DES include visible abnormalities of the cervix (cockscomb, hooded, or snub-nose exocervix or pseudopolyps) or vagina (fibrous bands, obliteration of the fornices, narrowing of the apices, or constriction rings). Daughters may also show increased tendency to suffer miscarriage or premature delivery. Abnormalities that require special measures for detection include adenosis, clear-cell carcinoma, cervical erosion, and mucosal abnormalities. Persons at risk require special counseling and monitoring. DES is still in use for purposes other than prevention of miscarriages. (9 Refs)

79. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.

Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

Current literature data on the cancer incidence among the users of oral contraceptive steroids (OCS) are reviewed. The use of OCS was shown to be associated with considerable increase of the incidence of breast cancer and cervical cancer. The largest increase in the incidence of breast and cervical cancer was observed in women 15-24 yr old who have a risk of double exposure to exogenous hormones. (29 Refs)

OTHER RELATED STUDIES

80. PINEAL REGION TUMORS: ENDOCRINOLOGICAL ASPECTS.

Giovannelli G
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Childs Brain; 9(3/4):267-273 1982

Relationships between pineal tumors and diabetes insipidus, precocious puberty, neuro-ophthalmologic signs, and other diagnostic indicators are discussed. Evidence supporting the view that the pineal gland and the superior cervical ganglia constitute an integration center for hormonal and neural signals includes production of two antigonadal principles in response to environment, feedback control of pineal activity by reproductive hormones, the role of norepinephrine released from pineal nerve endings in pineal metabolism, and the role of substances other than sex steroids in modifying pineal function. Study of the hormonal effects strictly dependent upon pineal function is hampered by the lack of confirmed cases and the problem of correlating endocrine signs and neuro-ophthalmological abnormalities with histopathologic abnormalities. Diabetes insipidus is an important early clinical sign of pineal region tumors. It is important to distinguish diabetes insipidus of central origin (CID) from nephrogenic diabetes insipidus and psychogenic polydipsia. Both differential diagnoses can be made by tests involving vasopressin levels. Data of polyuria and/or polydipsia should never be underestimated, especially in the male child. Not only diabetes mellitus should be excluded, but CID as well; once a diagnosis of CID is established and the rare familial form excluded, a tumor of the pineal region should be considered. In the presence of CID a thorough and global endocrinological evaluation should be done to demonstrate adenopituitary deficiency, one of the early clinical signs of pineal region tumors. (13 Refs)

81. PRIMARY HYPERALDOSTERONISM: DIFFERENTIATION BETWEEN ALDOSTERONE-PRODUCING ADENOMA AND IDIOPATHIC ADRENOCORTICAL HYPERPLASIA.

Wambach G, Helber A, Bonner G, Hummerich W, Konrads A, Meurer KA
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Dtsch Med Wochenschr; 107(24):923-927 1982

The regulation of aldosterone secretion by sodium restricted and enriched diet was assessed in 21 patients with primary aldosteronism for differentiation between unilateral aldosterone-producing adenoma and adrenocortical hyperplasia causing autonomous aldosterone hypersecretion. Compared to 10 patients with idiopathic adrenocortical hyperplasia, urinary aldosterone excretion after 4 days of sodium restricted diet was significantly higher in 11 patients with established adenoma (41.3 +-16.3 ug/24 hr vs 19.8 +-8.5 ug/24 hr; p less than 0.005). After 6 days of sodium loading these differences became even more obvious (35.3 +-14.0 ug/24 hr vs 12.7 +-3.7 ug/24 hr; p less than 0.0005). Sodium excretion did not influence aldosterone secretion in the adenoma group. In patients with hyperplasia both parameters showed a negative correlation (r =-0.522; p less than 0.001). Differentiation without overlap between both patient groups was achieved by comparison of the quotient of aldosterone excretion and serum potassium level during sodium enriched diet. (Author abstract) (20 Refs) (In GER)

82. TREATMENT OF HYPERPLASIA AND CARCINOMA IN SITU OF THE ENDOMETRIUM.

Kistner RW
Harvard Medical Sch., Boston, MA
Clin Obstet Gynecol; 25(1):63-74 1982

Therapy for hyperplasia and carcinoma in situ of the endometrium in patients of different ages is reported. The endocrine role of initiation and progression of endometrial cancer and endometrial hyperplasia and carcinoma of the endometrium are reviewed. Rationale for endocrine therapy is discussed. Case reports are presented illustrating the management of endometrial hyperplasia and carcinoma in situ in patients who desire children, in patients prior to hysterectomy, and in inoperable patients. Postpubescent patients with endometrial hyperplasia and carcinoma in situ should receive estrogen-progestin in artificial cycles for 6 mo and ovulation should be secured. Patients of child-bearing age should have ovulation secured with the use of cortisone, clomiphene, or wedge resection of the ovaries or estrogen-progestin, or progestin alone in artificial cycles for 6-12 mo. Premenopausal patients should have progestin artificial cycles until the age of 50-52 yr; hysterectomy should be performed in uncontrollable cases. Postmenopausal women should undergo hysterectomy; if inoperable, constant im progestin should be administered for 1 yr. Approx 10% of patients with atypical endometrial hyperplasia will eventually develop invasive carcinoma if untreated. Cells in glands that subsequently become cancerous exhibit abnormal DNA distribution and aneuploidy. (24 Refs)

83. SPONTANEOUS PRODUCTION OF ALPHA- AND BETA-INTERFERON IN HUMAN LYMPHOBLASTOID AND LYMPHOMA CELL LINES.

Adolf GR, Haas OA, Fischer P, Swetly P
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Arch Virol; 72(3):169-178 1982

A large number of human hematopoietic cell lines was examined for spontaneous production of interferon. Unconcentrated culture supernatants from 70 out of 71 B-lymphoblastoid cell lines contained considerable amounts of interferon (median titer 22 units per ml); a few lines produced more than 100 units/ml with peak values up to 500 units/ml. In contrast, only one B-lymphoma line out of 18 genuine lymphoma, myeloma, and leukemia cell lines tested spontaneously produced small amounts of interferon. Following treatment with 5-bromodeoxyuridine (BrdUrd), interferon was produced without further induction in most B-lymphoid cell lines, but not in any of the non-B, non-T, T-lymphoid or myeloid lines examined. Modulation of spontaneous interferon production by chemicals (sodium butyrate, dexamethasone, dimethylsulfoxide, a phorbol ester, and BrdUrd) was studied in more detail in three B-lymphoblastoid and four B-lymphoma cell lines. The patterns of responses observed were different for the action of different chemicals on a given cell line as well as between lymphoblastoid and lymphoma lines in general; furthermore, several lines of evidence suggest that chemicals can differentially influence spontaneous and virus-induced interferon production in a given cell line. The composition of spontaneously produced interferon was analyzed using antisera specific for HuIFN-alpha and HuIFN-beta. Interferons produced by untreated as well as BrdUrd-treated lymphoblastoid cells contained more than 95% IFN-alpha, whereas BrdUrd-treated lymphoma cells produced IFN-alpha as well as minor amounts (cell lines Namalwa and NC-37) or even over 90% of IFN-beta (Daudi). (Author abstract) (17 Refs)

84. EFFECTS OF GLUCOCORTICOIDS ON THE PHYSICAL AND BIOCHEMICAL PROPERTIES OF THE NORMAL NON-OEDEMATOUS BRAIN (MEETING ABSTRACT).

Bothe HW, Wallenfang TH, Hossmann KA, Schurmann K
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Acta Neurochir (Wien); 62:137 1982

In the following experiments, the influence of glucocorticoids on physical and biochemical parameters was studied in healthy nonedematous cats. Twelve male adult cats were randomly divided into 2 groups. Six animals were used as untreated controls and 6 cats were treated by twice daily intramuscular injections of 0.25 mg/kg dexamethasone (Decadron) over a period of 13 days. At the end of this period, the animals were anesthetized, tracheotomized, immobilized, and mechanically ventilated with room air. Ventricular pressure was measured by inserting a needle into the right lateral ventricle. After freezing the brain in situ with liquid nitrogen, tissue samples were taken from grey and white matter and processed for water and electrolyte content and substrates of energy-producing metabolism. We obtained the following results: After steroid therapy, the water content of the white matter decreased from 70.7 to 67.2%, and white matter potassium content increased from 197 to 249 meq/kg dry weight. Dexamethasone showed no effect on water and potassium content of grey matter nor on the sodium content or biochemical substrates of either grey or white matter. Furthermore, ventricular pressure remained constant in both experimental groups. The results obtained can be best explained by a selective reduction of extracellular fluid volume in white matter. (no Refs)

85. STUDIES IN NONSTEROIDAL ANTIESTROGENS AND RECEPTOR MEDIATED CYTOTOXICITY.

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Diss Abstr Int [B]; 42(9):3694-B 1982

The nonsteroidal antiestrogens Z-tamoxifen and Z-hydroxytamoxifen and their E isomers have been prepared in high specific activity tritium-labelled form. This permitted a comparative study of the metabolism and pharmacokinetics of Z-tamoxifen, an antiestrogen, and E-tamoxifen, an estrogen. It was found that different metabolites accumulate in the rat uterus following treatment with E- and Z-tamoxifen; this may account for their different endocrinological properties. The metabolism of the antiestrogens U-23, 469 and Cl-628 has also been studied using radio-labelled materials and the identity of their biologically-important metabolites confirmed chemically and chromatographically. A series of compounds designed to probe the importance of side-chain basicity in antiestrogens has been prepared, as has a series to elucidate the structural determinants necessary for evoking antiestrogen action; preliminary biological experiments with the compounds are reported. Several chemically-reactive tamoxifen analogs have been synthesized and evaluated biochemically and biologically as potential cytotoxic agents for tumors containing estrogen receptors. An aziridine analog of tamoxifen, tamiridine, is a binding site-specific and extremely potent irreversible inactivator of the estrogen receptor from lamb and rat uteri and MCF-7 human breast cancer cells. The inactivation is rapid and efficient with 1 nM tamiridine resulting by three hours in the inactivation of 0.2-0.9 nM of receptor. (no Refs)

86. EFFECTS OF ADRENAL CORTICAL STEROIDS AND OSMOTIC BLOOD-BRAIN BARRIER OPENING ON METHOTREXATE DELIVERY TO GLIOMAS IN THE RODENT: THE FACTOR OF THE BLOOD-BRAIN BARRIER.

Neuwelt EA, Barnett PA, Bigner DD, Frenkel EP
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Proc Natl Acad Sci USA; 79(14,part1):4420-4423 1982

The effect of adrenal cortical steroids and osmotic blood-brain barrier modification on methotrexate delivery to normal and glioma-bearing rats was studied. In animals with the avian sarcoma virus-induced glioma, osmotic blood-brain barrier modification resulted in significantly increased delivery of methotrexate to the tumor-bearing hemisphere (including the tumor, the brain around the tumor, and the brain distant to the tumor), compared to the nonmodified hemisphere or to control animals. The administration of adrenal steroids, followed by intracarotid methotrexate, resulted in slightly decreased chemotherapeutic agent (methotrexate) delivery to the tumor, the brain around the tumor, and the brain distant to the tumor. When adrenal steroids were given prior to barrier modification and methotrexate therapy, the level of methotrexate was significantly less in the tumor. These studies provide evidence that the blood-brain barrier exists in tumors and is a factor in drug delivery to tumors. Steroid administration greatly interferes with the enhancement of drug delivery to tumors that can be achieved with osmotic blood-brain barrier modification. (Author abstract) (17 Refs)

87. LONG-TERM EFFECTS OF INTERNAL IRRADIATION OF ENDOCRINE SYSTEM IN FEMALE RATS.

Dedov VI
Inst. Advanced Training for Physicians, Moscow, USSR
Izv Akad Nauk SSSR [Biol]; (3):454-458 1982

The long-term effects of internal irradiation of the endocrine system were studied in random-bred female rats. The animals received single iv injection of 75Se-selenomethionine (SM: 1.22 x 10(4) becquerel/g). The absorbed doses were 50 rads in the whole body and in the ovaries and 100 rads in the pituitary gland, thyroid, and adrenals. Animals were sacrificed on day 2 of the diestrus 1 and 2 wk, 1, 3, 6, 9, 12, and 18 mo after SM administration. Prolonged internal irradiation induced permanent estrus in 60% of the female rats. The female rats with permanent estrus developed mammary gland neoplasms (the latent period of mammary gland tumors was 5.5-7 mo for mature rats and 2.5 mo for old rats), thyroid and adrenal adenomas, pituitary gland prolactinomas, and uterine polyps. Development of endocrine neoplasms was associated with SM-induced elevation of blood levels of estrogens and prolactin and deficiency of thyroxine. (13 Refs) (In RUS)

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